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PATENT

Attorney Docket No. 002010-680

BE IT KNOWN, that we, Andrei W. KONRADI, Michael A. PLEISS, Eugene D. THORSETT, Susan ASHWELL, Gregory S. WELMAKER, Anthony KREFT, Dimitrios SARANTAKIS, Darren B. DRESSEN, Francine S. GRANT, Christopher SEMKO and YING-ZI XU have invented new and useful improvements in:

**ALPHA AMINO ACID DERIVATIVES--INHIBITORS OF  
LEUKOCYTE ADHESION MEDIATED BY VLA-4**

002010-680

**ALPHA AMINO ACID DERIVATIVES-- INHIBITORS OF  
LEUKOCYTE ADHESION MEDIATED BY VLA-4**

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**CROSS REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of U.S. Patent Application Serial  
No. 60/220,132, filed July 21, 2000, the disclosures of which are incorporated  
herein by reference in their entirety.

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**BACKGROUND OF THE INVENTION**

Field of the Invention

This invention relates to certain alpha amino acid derivatives which  
inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by  
VLA-4.

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References

The following publications, patents and patent applications are cited  
in this application as superscript numbers:

20

- <sup>1</sup> Hemler and Takada, *European Patent Application Publication*  
*No. 330,506*, published August 30, 1989
- <sup>2</sup> Elices, et al., *Cell*, 60:577-584 (1990)
- <sup>3</sup> Springer, *Nature*, 346:425-434 (1990)
- <sup>4</sup> Osborn, *Cell*, 62:3-6 (1990)
- <sup>5</sup> Vedder, et al., *Surgery*, 106:509 (1989)
- <sup>6</sup> Pretolani, et al., *J. Exp. Med.*, 180:795 (1994)
- <sup>7</sup> Abraham, et al., *J. Clin. Invest.*, 93:776 (1994)
- <sup>8</sup> Mulligan, et al., *J. Immunology*, 150:2407 (1993)
- <sup>9</sup> Cybulsky, et al., *Science*, 251:788 (1991)

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- 5 10 Li, et al., *Arterioscler. Thromb.*, 13:197 (1993)
- 11 Sasseville, et al., *Am. J. Path.*, 144:27 (1994)
- 12 Yang, et al., *Proc. Nat. Acad. Science (USA)*, 90:10494  
10 (1993)
- 13 Burkly, et al., *Diabetes*, 43:529 (1994)
- 14 Baron, et al., *J. Clin. Invest.*, 93:1700 (1994)
- 15 Hamann, et al., *J. Immunology*, 152:3238 (1994)
- 16 Yednock, et al., *Nature*, 356:63 (1992)
- 17 Baron, et al., *J. Exp. Med.*, 177:57 (1993)
- 18 van Dinther-Janssen, et al., *J. Immunology*, 147:4207 (1991)
- 19 van Dinther-Janssen, et al., *Annals. Rheumatic Dis.*, 52:672  
25 (1993)
- 20 Elices, et al., *J. Clin. Invest.*, 93:405 (1994)
- 21 Postigo, et al., *J. Clin. Invest.*, 89:1445 (1991)
- 22 Paul, et al., *Transpl. Proceed.*, 25:813 (1993)
- 23 Okarhara, et al., *Can. Res.*, 54:3233 (1994)
- 24 Paavonen, et al., *Int. J. Can.*, 58:298 (1994)
- 25 Schadendorf, et al., *J. Path.*, 170:429 (1993)
- 26 Bao, et al., *Diff.*, 52:239 (1993)
- 40 27 Lauri, et al., *British J. Cancer*, 68:862 (1993)
- 28 Kawaguchi, et al., *Japanese J. Cancer Res.*, 83:1304 (1992)
- 45 29 Kogan, et al., *U.S. Patent No. 5,510,332*, issued April 23,  
1996
- 30 30 International Patent Appl. Publication No. WO 96/01644

5 All of the above publications, patents and patent applications are  
herein incorporated by reference in their entirety to the same extent as if  
each individual publication, patent or patent application was specifically and  
individually indicated to be incorporated by reference in its entirety.

10 State of the Art

VLA-4 (also referred to as  $\alpha_4\beta_1$  integrin and CD49d/CD29), first  
identified by Hemler and Takada<sup>1</sup> is a member of the  $\beta_1$  integrin family of  
cell surface receptors, each of which comprises two subunits, an  $\alpha$  chain and  
a  $\beta$  chain. VLA-4 contains an  $\alpha_4$  chain and a  $\beta_1$  chain. There are at least  
15 nine  $\beta_1$  integrins, all sharing the same  $\beta_1$  chain and each having a distinct  $\alpha$   
chain. These nine receptors all bind a different complement of the various  
cell matrix molecules, such as fibronectin, laminin, and collagen. VLA-4,  
for example, binds to fibronectin. VLA-4 also binds non-matrix molecules  
that are expressed by endothelial and other cells. These non-matrix  
20 molecules include VCAM-1, which is expressed on cytokine-activated  
human umbilical vein endothelial cells in culture. Distinct epitopes of VLA-  
4 are responsible for the fibronectin and VCAM-1 binding activities and each  
activity has been shown to be inhibited independently.<sup>2</sup>

25 Intercellular adhesion mediated by VLA-4 and other cell surface  
receptors is associated with a number of inflammatory responses. At the site  
of an injury or other inflammatory stimulus, activated vascular endothelial  
cells express molecules that are adhesive for leukocytes. The mechanics of  
leukocyte adhesion to endothelial cells involves, in part, the recognition and  
30 binding of cell surface receptors on leukocytes to the corresponding cell  
surface molecules on endothelial cells. Once bound, the leukocytes migrate  
across the blood vessel wall to enter the injured site and release chemical  
mediators to combat infection. For reviews of adhesion receptors of the  
immune system, *see*, for example, Springer<sup>3</sup> and Osborn<sup>4</sup>.



5           Inflammatory brain disorders, such as experimental autoimmune  
encephalomyelitis (EAE), multiple sclerosis (MS) and meningitis, are  
examples of central nervous system disorders in which the  
endothelium/leukocyte adhesion mechanism results in destruction to  
otherwise healthy brain tissue. Large numbers of leukocytes migrate across  
10   the blood brain barrier (BBB) in subjects with these inflammatory diseases.  
The leukocytes release toxic mediators that cause extensive tissue damage  
resulting in impaired nerve conduction and paralysis.

15           In other organ systems, tissue damage also occurs via an adhesion  
mechanism resulting in migration or activation of leukocytes. For example,  
it has been shown that the initial insult following myocardial ischemia to  
heart tissue can be further complicated by leukocyte entry to the injured  
tissue causing still further insult (Vedder et al.<sup>5</sup>). Other inflammatory or  
medical conditions mediated by an adhesion mechanism include, by way of  
20   example, asthma<sup>6-8</sup>, Alzheimer's disease, atherosclerosis<sup>9-10</sup>, AIDS  
dementia<sup>11</sup>, diabetes<sup>12-14</sup> (including acute juvenile onset diabetes),  
inflammatory bowel disease<sup>15</sup> (including ulcerative colitis and Crohn's  
disease), multiple sclerosis<sup>16-17</sup>, rheumatoid arthritis<sup>18-21</sup>, tissue  
transplantation<sup>22</sup>, tumor metastasis<sup>23-28</sup>, meningitis, encephalitis, stroke, and  
25   other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis,  
myocardial ischemia and acute leukocyte-mediated lung injury such as that  
which occurs in adult respiratory distress syndrome.

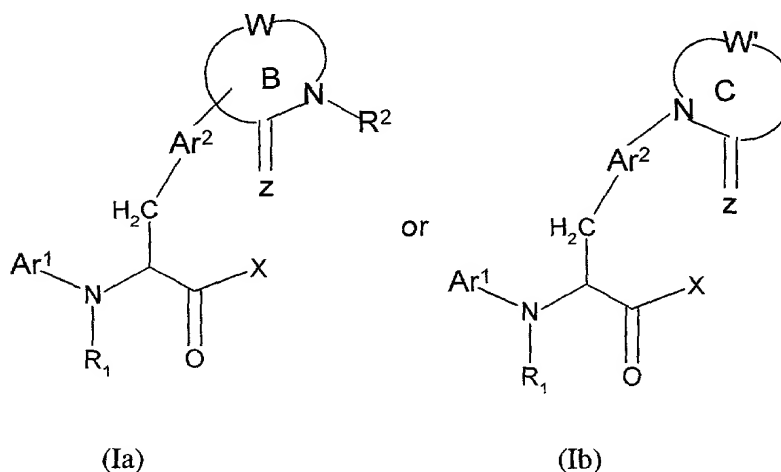
30           In view of the above, assays for determining the VLA-4 level in a  
biological sample containing VLA-4 would be useful, for example, to  
diagnosis VLA-4 mediated conditions. Additionally, despite these advances  
in the understanding of leukocyte adhesion, the art has only recently  
addressed the use of inhibitors of adhesion in the treatment of inflammatory

5 brain diseases and other inflammatory conditions<sup>29,30</sup>. The present invention addresses these and other needs.

# SUMMARY OF THE INVENTION

10 This invention provides compounds which bind to VLA-4. Such compounds can be used, for example, to assay for the presence of VLA-4 in a sample and in pharmaceutical compositions to inhibit cellular adhesion mediated by VLA-4, for example, binding of VCAM-1 to VLA-4. The compounds of this invention have a binding affinity to VLA-4 as expressed by an IC<sub>50</sub> of about 15  $\mu$ M or less (as measured using the procedures described in Example A below).

15 Accordingly, in one of its composition aspects, this invention is directed to a compound of Formula (Ia) or (Ib):



wherein:

30 Ar<sup>1</sup> is an aryl, heteroaryl, cycloalkyl, or heterocyclic group wherein said aryl, heteroaryl, cycloalkyl, or heterocyclic group is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino,

5 substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl,  
aminocarbonylamino, aminothiocabonylamino, aminocarbonyloxy, aryl,  
substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted  
aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl,  
substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl,  
10 substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl,  
substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl,  
thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted  
heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted  
cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy,  
15 substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino,  
-OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-substituted  
aryl, -OS(O)<sub>2</sub>-heteroaryl, -OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-  
heterocyclic, -OS(O)<sub>2</sub>-substituted heterocyclic, -OSO<sub>2</sub>-NRR where each R is  
independently hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl, -NRS(O)<sub>2</sub>-substituted  
20 alkyl, -NRS(O)<sub>2</sub>-aryl, -NRS(O)<sub>2</sub>-substituted aryl, -NRS(O)<sub>2</sub>-heteroaryl,  
-NRS(O)<sub>2</sub>-substituted heteroaryl, -NRS(O)<sub>2</sub>-heterocyclic, -NRS(O)<sub>2</sub>-  
substituted heterocyclic, -NRS(O)<sub>2</sub>-NR-alkyl, -NRS(O)<sub>2</sub>-NR-substituted  
alkyl, -NRS(O)<sub>2</sub>-NR-aryl, -NRS(O)<sub>2</sub>-NR-substituted aryl, -NRS(O)<sub>2</sub>-NR-  
heteroaryl, -NRS(O)<sub>2</sub>-NR-substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-heterocyclic,  
25 -NRS(O)<sub>2</sub>-NR-substituted heterocyclic where R is hydrogen or alkyl,  
-N[S(O)<sub>2</sub>-R']<sub>2</sub> and -N[S(O)<sub>2</sub>-NR']<sub>2</sub> where each R' is independently selected  
from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl,  
heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

R<sup>1</sup> is selected from the group consisting of hydrogen, alkyl,  
30 substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted  
cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl,  
heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Ar<sup>2</sup> is an aryl or heteroaryl group optionally substituted, in addition  
to ring B or C, with one or two substituent(s) selected from the group

consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, aminoacyl, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, and substituted alkylsulfonyl;

Z is -O- or -S-;

B is a group wherein W, together with  $-C(=Z)NR^2-$ , forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and  $-SO_n-$  (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylene dioxy, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano,

acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

$R^2$  is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl;

C is a group wherein W', together with  $-C(=Z)N-$ , forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and  $-SO_n-$  (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, alkylenedioxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, nitro, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

X is selected from the group consisting of hydroxyl, alkoxy,

5 substituted alkoxy, alkenoxy, substituted alkenoxy, cycloalkoxy, substituted  
cycloalkoxy, cycloalkenoxy, substituted cycloalkenoxy, aryloxy, substituted  
aryloxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy,  
substituted heterocyclyloxy and -NR''R'' where each R'' is independently  
10 selected from the group consisting of hydrogen, alkyl, substituted alkyl,  
alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl,  
substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and  
substituted heterocyclic;

and enantiomers, diastereomers and pharmaceutically acceptable salts  
thereof;

15 and further wherein the compound of Formula I has a binding affinity  
to VLA-4 as expressed by an IC<sub>50</sub> of about 15 $\mu$ M or less.

In a preferred embodiment, in compound (Ia), B is either:

(a) a group wherein W, together with -C(=Z)NR<sup>2</sup>- where Z is -O-,  
20 forms an unsaturated heterocyclic group containing 3 or 4 carbon atoms and  
0 or 1 additional nitrogen atoms and further wherein the unsaturated  
heterocyclic group is optionally substituted, in addition to the R<sup>2</sup> group, with  
1 or 2 substituents selected from the group consisting of alkyl, alkoxy,  
substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono  
25 or dialkylamino. Preferably B is 2-pyridone, (e.g., 2-pyridon-3-yl, 2-  
pyridon-4-yl, etc.,) or 6-pyrimidone (e.g., 6-pyrimidon-5-yl, etc.,) that is  
optionally substituted, in addition to the R<sup>2</sup> group, with 1 or 2 substituents  
selected from the group consisting of alkyl, alkoxy, substituted alkoxy,  
alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino,  
30 more preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy,  
allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl  
group in said methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may  
be optionally substituted with one, two or three substituents selected from  
the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide,

alkylsulfone, halo, alkylamino, dialkylamino, amino, aminoacyl, preferably, hydroxy, methoxy, ethoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings R<sup>2</sup> is alkyl, preferably methyl; or

(b) a group wherein W, together with -C(=Z)NR<sup>2</sup>- where Z is -O-, forms a saturated or unsaturated heterocyclic group containing 3 or 4 carbon atoms and 0 or 1 additional nitrogen atoms wherein said saturated or unsaturated heterocyclic group is fused to a heterocyclic ring selected from the group consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran, dihydropyran, furan, oxazolidine, oxazole, isoxazole, oxazolidinone, oxathiolane, and 1,3-dioxolan-2-one and wherein the resulting fused ring is optionally substituted, in addition to the R<sup>2</sup> group, on any ring atom capable of substitution with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino. Preferably B is 2-pyridone or 6-pyrimidone that is fused to a heterocyclic ring selected from the group consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran, dihydropyran, furan, oxazolidine, oxazole, isoxazole, oxazolidinone, oxathiolane, and 1,3-dioxolan-2-one, and wherein the resulting fused ring is optionally substituted, in addition to the R<sup>2</sup> group, on any ring atom capable of substitution with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino, more preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl group in said methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may be optionally substituted with one, two or three substituents selected from the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino, dialkylamino, amino, aminoacyl, preferably,

5 hydroxy, methoxy, ethoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings  $R^2$  is alkyl, preferably methyl.

10 In a preferred embodiment, in compound (Ib), C is either:

- (a) a group wherein  $W'$ , together with  $-C(=Z)N-$  where Z is  $-O-$ , forms an unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms and further the wherein the unsaturated heterocyclic group is optionally substituted, in addition to the  $R^2$  group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino. Preferably C is 2-pyridon-1-yl or 6-pyrimidon-1-yl that is optionally substituted, in addition to the  $R^2$  group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino, more preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl group in said methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may be optionally substituted with one, two or three substituents selected from the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino, dialkylamino, amino, aminoacyl, preferably, hydroxy, methoxy, ethoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings  $R^2$  is alkyl, preferably methyl; or
- (b) a group wherein  $W'$ , together with  $-C(=Z)N-$  where Z is  $-O-$ , forms a saturated or unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms wherein said saturated or unsaturated heterocyclic group is fused to a heterocyclic ring selected from the group



5 consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran,  
dihydropyran, furan, oxazolidine, oxazole, isoxazole, oxazolidinone,  
oxathiolane, and 1,3-dioxolan-2-one and wherein the resulting fused ring is  
optionally substituted, in addition to the  $R^2$  group, on any ring atom capable  
of substitution with 1 or 2 substituents selected from the group consisting of  
10 alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo,  
hydroxy, mono or dialkylamino. Preferably C is 2-pyridon-1-yl or 6-  
pyrimidon-1-yl that is fused to a heterocyclic ring selected from the group  
consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran,  
dihydropyran, furan, oxazolidine, oxazole, isoxazole, oxazolidinone,  
15 oxathiolane, and 1,3-dioxolan-2-one, and wherein the resulting fused ring is  
optionally substituted, in addition to the  $R^2$  group, on any ring atom capable  
of substitution with 1 or 2 substituents selected from the group consisting of  
alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo,  
hydroxy, mono or dialkylamino, more preferably methyl, ethyl, propyl,  
20 methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy (wherein the  
methyl, ethyl, propyl, butyl, and allyl group in said methoxy, ethoxy,  
propoxy, butoxy, allyloxy, butenyloxy may be optionally substituted with  
one, two or three substituents selected from the group consisting of hydroxy,  
alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino,  
25 dialkylamino, amino, aminoacyl, preferably, hydroxy, methoxy, ethoxy,  
methylthio, methylsulfane, methylsulfone, fluoro, methylamino,  
dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy,  
methylamino, or dimethylamino. More preferably in the above rings  $R^2$  is  
alkyl, preferably methyl.

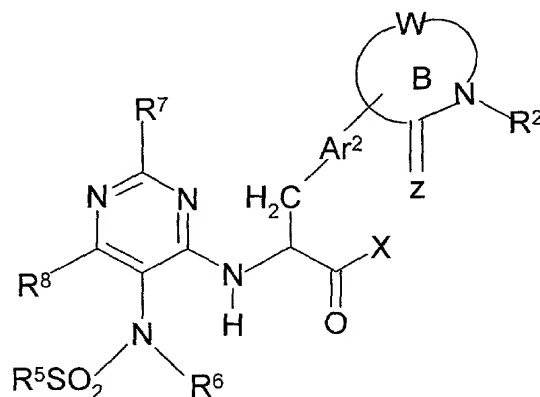
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In another preferred embodiment,  $Ar^1$  in compounds (Ia) and (Ib) is a  
heteroaryl group optionally substituted with 1 to 3 substituents selected from  
the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy,  
amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted

aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen, preferably 1-oxo-1,2,5-thiadiazole, 1,1-dioxo-1,2,5-thiadiazole, 1,3,5-triazine, pyridazine, pyrimidine or pyrazine substituted with above substituents; more preferably pyridazine, pyrimidine or pyrazine wherein the pyridazine, pyrimidine or pyrazine ring is optionally substituted with 1 to 3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen.

In yet another preferred embodiment,  $Ar^2$  in compounds (Ia) and (Ib) is phenyl.

In the above preferred embodiments, a more preferred group of compounds is that wherein X is hydroxyl and  $R^1$  is hydrogen.

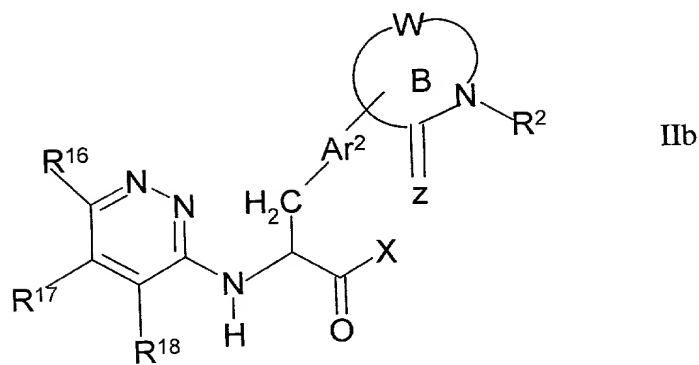
In yet another preferred embodiment, this invention is directed to compounds of formula IIa, IIb, IIc, IId, or IIe:



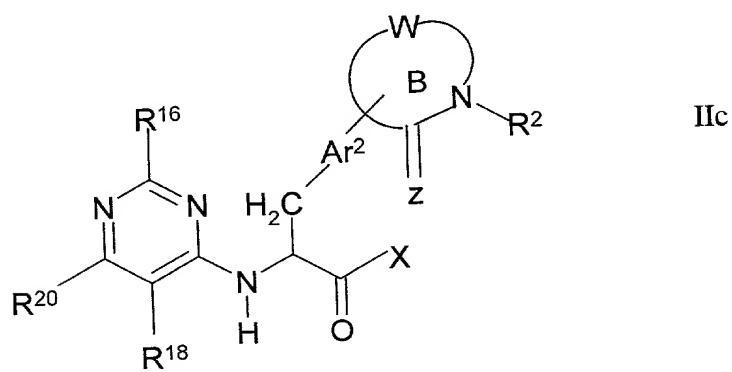
IIa

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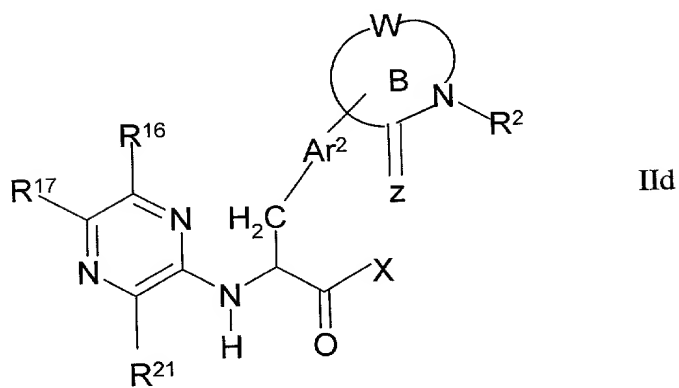
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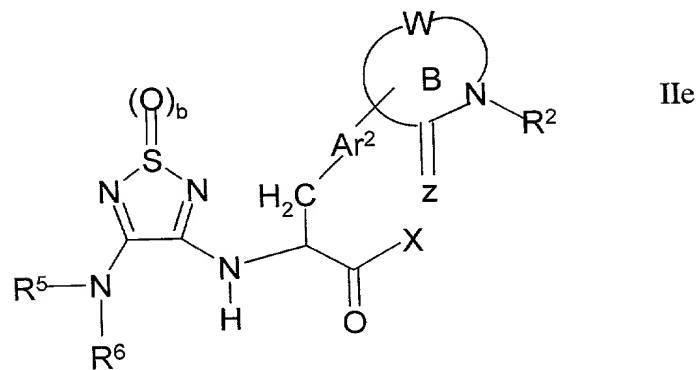


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5 wherein

X is hydroxyl or alkoxy;

Ar<sup>2</sup> is an aryl or heteroaryl group optionally substituted, in addition to ring B, with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, and substituted alkylsulfonyl;

R<sup>5</sup> is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

R<sup>6</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -SO<sub>2</sub>R<sup>10</sup> where R<sup>10</sup> is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

5           R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

10           R<sup>18</sup> is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

15           R<sup>20</sup> is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

20           R<sup>21</sup> is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic;

*b* is 1 or 2; and

25           B is a group wherein W, together with -C(=Z)NR<sup>2</sup>-, forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and -SO<sub>n</sub>- (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures  
30           are optionally substituted with 1 to 3 substituents selected from the group consisting of with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino,

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5 N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylene dioxy,  
(alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-  
alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted  
alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl,  
cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano,  
10 acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio,  
substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl,  
substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted  
heteroaryl;

R<sup>2</sup> is selected from the group consisting of alkyl, substituted alkyl,  
15 aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl,  
substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl; and  
and enantiomers, diastereomers and pharmaceutically acceptable salts  
thereof.

20 Preferably, the compound is selected from formula IIc, IId or IIe.

In the above compounds II(a-e), B is either:

(a) a group wherein W, together with -C(=Z)NR<sup>2</sup>- where Z is -O-,  
forms an unsaturated heterocyclic group containing 2 to 4 carbon atoms and  
25 0 to 2 additional nitrogen atoms and further the wherein the unsaturated  
heterocyclic group is optionally substituted, in addition to the R<sup>2</sup> group, with  
1 or 2 substituents selected from the group consisting of alkyl, alkoxy,  
substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono  
or dialkylamino. Preferably B is 2-pyridone, (e.g., 2-pyridon-3-yl, 2-  
30 pyridon-4-yl, etc.), or 6-pyrimidone (e.g., 6-pyrimidon-5-yl, etc.), that is  
optionally substituted, in addition to the R<sup>2</sup> group, with 1 or 2 substituents  
selected from the group consisting of alkyl, alkoxy, substituted alkoxy,  
alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino,  
more preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy,

allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl group in said methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may be optionally substituted with one, two or three substituents selected from the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino, dialkylamino, amino, aminoacyl, preferably, hydroxy, methoxy, ethoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings R<sup>2</sup> is alkyl, preferably methyl; or

(b) a group wherein W, together with -C(=Z)NR<sup>2</sup>- where Z is -O-, forms a saturated or unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms wherein said saturated or unsaturated heterocyclic group is fused to a heterocyclic ring selected from the group consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran, dihydropyran, furan, oxazolidine, oxazole, isoxazole, oxazolidinone, oxathiolane, and 1,3-dioxolan-2-one and wherein the resulting fused ring is optionally substituted, in addition to the R<sup>2</sup> group, on any ring atom capable of substitution with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino. Preferably B is 2-pyridone or 6-pyrimidone that is fused to a heterocyclic ring selected from the group consisting of dioxolane, dioxane, homodioxane, oxetane, tetrahydrofuran, dihydropyran, furan, oxazolidine, oxazole, isoxazole, oxazolidinone, oxathiolane, and 1,3-dioxolan-2-one, and wherein the resulting fused ring is optionally substituted, in addition to the R<sup>2</sup> group, on any ring atom capable of substitution with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino, preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl group in said

methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may be optionally substituted with one, two or three substituents selected from the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino, dialkylamino, amino, aminoacyl, preferably, hydroxy, methoxy, ethoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings  $R^2$  is alkyl, preferably methyl and X is hydroxyl.

In the above compounds II(a-e),  $Ar^2$  is preferably phenyl.

Within the above preferred groups of II(a-e), a more preferred group of compounds is that wherein  $R^5$  is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl. Even more preferably  $R^5$  is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, *n*-hexyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-( $CH_3C(O)NH$ -)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[ $CH_3SC(=NH)$ ]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[ $H_2NC(S)$ ]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl;

$R^{16}$  is substituted amino;



5           R<sup>6</sup>, R<sup>17</sup> and/or R<sup>20</sup> are hydrogen; and  
          R<sup>18</sup> and/or R<sup>21</sup> are alkyl, substituted alkyl, aryl, or substituted aryl.

10           In a second aspect, this invention provides pharmaceutical  
          compositions comprising a pharmaceutically acceptable carrier and a  
          therapeutically effective amount of the compounds defined herein.

15           In a third aspect, this invention is directed to a method for treating a  
          disease mediated by VLA-4 in a patient, which method comprises  
          administering a pharmaceutical composition comprising a pharmaceutically  
          acceptable carrier and a therapeutically effective amount of compounds  
          defined herein.

20           In the above compounds, when X is other than -OH or  
          pharmaceutical salts thereof, X is preferably a substituent which will convert  
          (e.g., hydrolyze, metabolize, etc.) *in vivo* to a compound where X is -OH or  
          a salt thereof. Accordingly, suitable X groups are any art recognized  
          pharmaceutically acceptable groups which will hydrolyze or otherwise  
          convert *in vivo* to a hydroxyl group or a salt thereof including, by way of  
          example, esters (X is alkoxy, substituted alkoxy, cycloalkoxy, substituted  
25           cycloalkoxy, alkenoxy, substituted alkenoxy, cycloalkenoxo, substituted  
          cycloalkenoxo, aryloxy, substituted aryloxy, heteroaryloxy, substituted  
          heteroaryloxy, heterocycloxy, substituted heterocycloxy, and the like).

30           This invention also provides methods for binding VLA-4 in a  
          biological sample which method comprises contacting the biological sample  
          with a compound of this invention under conditions wherein said compound  
          binds to VLA-4.

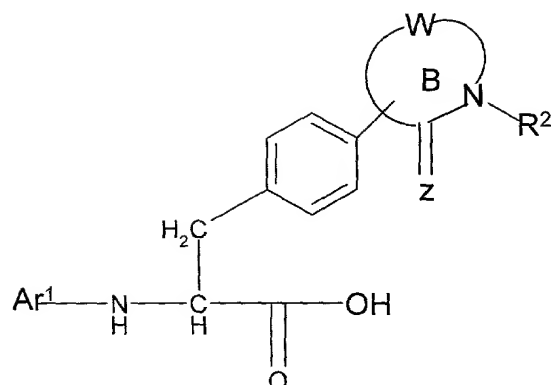
5           The compounds and pharmaceutical compositions of this invention  
are useful for treating disease conditions mediated by VLA-4 or leucocyte  
adhesion. Such disease conditions include, by way of example, asthma,  
Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including  
10 acute juvenile onset diabetes), inflammatory bowel disease (including  
ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid  
arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis,  
stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis,  
psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury  
such as that which occurs in adult respiratory distress syndrome.

15           Other disease conditions include, but are not limited to, inflammatory  
conditions such as erythema nodosum, allergic conjunctivitis, optic neuritis,  
uveitis, allergic rhinitis, Ankylosing spondylitis, psoriatic arthritis,  
vasculitis, Reiter's syndrome, systemic lupus erythematosus, progressive  
20 systemic sclerosis, polymyositis, dermatomyositis, Wegner's  
granulomatosis, aortitis, sarcoidosis, lymphocytopenia, temporal arteritis,  
pericarditis, myocarditis, congestive heart failure, polyarteritis nodosa,  
hypersensitivity syndromes, allergy, hypereosinophilic syndromes, Churg-  
Strauss syndrome, chronic obstructive pulmonary disease, hypersensitivity  
25 pneumonitis, chronic active hepatitis, interstitial cystitis, autoimmune  
endocrine failure, primary biliary cirrhosis, autoimmune aplastic anemia,  
chronic persistent hepatitis and thyroiditis.

30           In a preferred embodiment, the disease condition mediated by VLA-4  
is an inflammatory disease.

          Preferred compounds of this invention include those set forth in the  
Table below:

Table I



Cpd #	A	B
1	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-CF <sub>3</sub> CH <sub>2</sub> ]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
2	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-CF <sub>3</sub> CH <sub>2</sub> ]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
3	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-CF <sub>3</sub> CH <sub>2</sub> ]pyrimidin-4-yl	1-n-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
4	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-CF <sub>3</sub> CH <sub>2</sub> ]pyrimidin-4-yl	1-i-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
5	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-CF <sub>3</sub> CH <sub>2</sub> ]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
6	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-CF <sub>3</sub> CH <sub>2</sub> ]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
7	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-CF <sub>3</sub> CH <sub>2</sub> ]pyrimidin-4-yl	1-n-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
8	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-CF <sub>3</sub> CH <sub>2</sub> ]pyrimidin-4-yl	1-i-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
9	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> ) <sub>2</sub> CH]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl

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10	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> ) <sub>2</sub> CH]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
11	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> ) <sub>2</sub> CH]pyrimidin-4-yl	1-n-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
12	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> ) <sub>2</sub> CH]pyrimidin-4-yl	1-i-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
13	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> ) <sub>2</sub> CH]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
14	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> ) <sub>2</sub> CH]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
15	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> ) <sub>2</sub> CH]pyrimidin-4-yl	1-n-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
16	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> ) <sub>2</sub> CH]pyrimidin-4-yl	1-i-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
17	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CH]-pyrimidin-4-yl	1-i-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
18	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CH]-pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
19	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CH]-pyrimidin-4-yl	1-n-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
20	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CH]-pyrimidin-4-yl	1-i-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
21	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CH]-pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
22	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CH]-pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
23	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CH]-pyrimidin-4-yl	1-n-C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl

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24	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CH]- pyrimidin-4-yl	1- <i>i</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5- yl
25	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isoxazol-4- yl)]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
26	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isoxazol-4- yl)]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
27	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isoxazol-4- yl)]pyrimidin-4-yl	1- <i>n</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
28	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isoxazol-4- yl)]pyrimidin-4-yl	1- <i>i</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
29	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isoxazol-4- yl)]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
30	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isoxazol-4- yl)]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
31	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isoxazol-4- yl)]pyrimidin-4-yl	1- <i>n</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5- yl
32	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isoxazol-4- yl)]pyrimidin-4-yl	1- <i>i</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5- yl
33	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(1,3,5-triCH <sub>3</sub> pyrazol- 4-yl)]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
34	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(1,3,5-triCH <sub>3</sub> pyrazol- 4-yl)]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
35	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(1,3,5-triCH <sub>3</sub> pyrazol- 4-yl)]pyrimidin-4-yl	1- <i>n</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
36	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(1,3,5-triCH <sub>3</sub> pyrazol- 4-yl)]pyrimidin-4-yl	1- <i>i</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
37	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(1,3,5-triCH <sub>3</sub> pyrazol- 4-yl)]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl

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38	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(1,3,5-triCH <sub>3</sub> pyrazol-4-yl)]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
39	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(1,3,5-triCH <sub>3</sub> pyrazol-4-yl)]pyrimidin-4-yl	1- <i>n</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
40	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(1,3,5-triCH <sub>3</sub> pyrazol-4-yl)]pyrimidin-4-yl	1- <i>i</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
41	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isothiazol-4-yl)]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
42	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isothiazol-4-yl)]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
43	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isothiazol-4-yl)]pyrimidin-4-yl	1- <i>n</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
44	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isothiazol-4-yl)]pyrimidin-4-yl	1- <i>i</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-2-pyridon-3-yl
45	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isothiazol-4-yl)]pyrimidin-4-yl	1-CH <sub>3</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
46	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isothiazol-4-yl)]pyrimidin-4-yl	1-C <sub>2</sub> H <sub>5</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
47	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isothiazol-4-yl)]pyrimidin-4-yl	1- <i>n</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl
48	[2-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-5-(3,5-diCH <sub>3</sub> isothiazol-4-yl)]pyrimidin-4-yl	1- <i>i</i> -C <sub>3</sub> H <sub>7</sub> -4-CH <sub>3</sub> O-6-pyrimidon-5-yl

and are named as follows:

*N*-(2-(*N,N*-diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

5 *N*-(2-(*N,N*-diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-  
(1-propyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-  
(1-isopropyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

10 *N*-(2-(*N,N*-diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-  
(1-methyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-  
(1-ethyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-  
(1-propyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

15 *N*-(2-(*N,N*-diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-  
(1-isopropyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2-methylpropyl)pyrimidin-4-yl)-L-4'-(1-  
methyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

20 *N*-(2-(*N,N*-diethylamino)-5-(2-methylpropyl)pyrimidin-4-yl)-L-4'-(1-  
ethyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2-methylpropyl)pyrimidin-4-yl)-L-4'-(1-  
propyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2-methylpropyl)pyrimidin-4-yl)-L-4'-(1-  
isopropyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

25 *N*-(2-(*N,N*-diethylamino)-5-(2-methylpropyl)pyrimidin-4-yl)-L-4'-(1-  
methyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2-methylpropyl)pyrimidin-4-yl)-L-4'-(1-  
ethyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

30 *N*-(2-(*N,N*-diethylamino)-5-(2-methylpropyl)pyrimidin-4-yl)-L-4'-(1-  
propyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(2-methylpropyl)pyrimidin-4-yl)-L-4'-(1-  
isopropyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1-ethylpropyl)pyrimidin-4-yl)-L-4'-(1-  
methyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

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5 *N*-(2-(*N,N*-diethylamino)-5-(1-ethylpropyl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1-ethylpropyl)pyrimidin-4-yl)-L-4'-(1-propyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

10 *N*-(2-(*N,N*-diethylamino)-5-(1-ethylpropyl)pyrimidin-4-yl)-L-4'-(1-isopropyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1-ethylpropyl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1-ethylpropyl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

15 *N*-(2-(*N,N*-diethylamino)-5-(1-ethylpropyl)pyrimidin-4-yl)-L-4'-(1-propyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1-ethylpropyl)pyrimidin-4-yl)-L-4'-(1-isopropyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

20 *N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisoxazol-4-yl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisoxazol-4-yl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisoxazol-4-yl)pyrimidin-4-yl)-L-4'-(1-propyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

25 *N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisoxazol-4-yl)pyrimidin-4-yl)-L-4'-(1-isopropyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisoxazol-4-yl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

30 *N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisoxazol-4-yl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisoxazol-4-yl)pyrimidin-4-yl)-L-4'-(1-propyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisoxazol-4-yl)pyrimidin-4-yl)-L-4'-(1-isopropyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

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5 *N*-(2-(*N,N*-diethylamino)-5-(1,3,5-trimethylpyrazol-4-yl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1,3,5-trimethylpyrazol-4-yl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

10 *N*-(2-(*N,N*-diethylamino)-5-(1,3,5-trimethylpyrazol-4-yl)pyrimidin-4-yl)-L-4'-(1-propyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1,3,5-trimethylpyrazol-4-yl)pyrimidin-4-yl)-L-4'-(1-isopropyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1,3,5-trimethylpyrazol-4-yl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

15 *N*-(2-(*N,N*-diethylamino)-5-(1,3,5-trimethylpyrazol-4-yl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(1,3,5-trimethylpyrazol-4-yl)pyrimidin-4-yl)-L-4'-(1-propyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

20 *N*-(2-(*N,N*-diethylamino)-5-(1,3,5-trimethylpyrazol-4-yl)pyrimidin-4-yl)-L-4'-(1-isopropyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisothiazol-4-yl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisothiazol-4-yl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

25 *N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisothiazol-4-yl)pyrimidin-4-yl)-L-4'-(1-propyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisothiazol-4-yl)pyrimidin-4-yl)-L-4'-(1-isopropyl-4-methoxy-2-pyridon-3-yl)phenylalanine;

30 *N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisothiazol-4-yl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisothiazol-4-yl)pyrimidin-4-yl)-L-4'-(1-ethyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine;

*N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisothiazol-4-yl)pyrimidin-4-yl)-L-4'-(1-propyl-4-methoxy-6-pyrimidon-5-yl)phenylalanine; and

5                    *N*-(2-(*N,N*-diethylamino)-5-(3,5-dimethylisothiazol-4-yl)pyrimidin-4-yl)-L-4'-(1-isopropyl-4-methoxy-6-pyrimidin-5-yl)phenylalanine.

### DETAILED DESCRIPTION OF THE INVENTION

As above, this invention relates to compounds which inhibit leukocyte  
10 adhesion and, in particular, leukocyte adhesion mediated by VLA-4.  
However, prior to describing this invention in further detail, the following  
terms will first be defined.

#### Definitions

15                    As used herein, "alkyl" refers to alkyl groups preferably having from  
1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is  
exemplified by groups such as methyl, t-butyl, n-heptyl, octyl and the like.

"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 10  
20 carbon atoms, having from 1 to 5 substituents selected from the group  
consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino,  
acyloxy, amino, amidino, alkyl amidino, thioamidino, aminoacyl,  
aminocarbonylamino, aminothiocabonylamino, aminocarbonyloxy, aryl,  
substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted  
25 aryloxyaryl, cyano, halogen, hydroxyl, nitro, carboxyl, carboxylalkyl,  
carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted  
cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl,  
carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted  
heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone,  
30 thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl,  
thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted  
thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl,  
substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy,  
substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy,

heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino,  $-\text{OS}(\text{O})_2\text{-alkyl}$ ,  $-\text{OS}(\text{O})_2\text{-substituted alkyl}$ ,  $-\text{OS}(\text{O})_2\text{-aryl}$ ,  $-\text{OS}(\text{O})_2\text{-substituted aryl}$ ,  $-\text{OS}(\text{O})_2\text{-heteroaryl}$ ,  $-\text{OS}(\text{O})_2\text{-substituted heteroaryl}$ ,  $-\text{OS}(\text{O})_2\text{-heterocyclic}$ ,  $-\text{OS}(\text{O})_2\text{-substituted heterocyclic}$ ,  $-\text{OSO}_2\text{-NRR}$  where R is hydrogen or alkyl,  $-\text{NRS}(\text{O})_2\text{-alkyl}$ ,  $-\text{NRS}(\text{O})_2\text{-substituted alkyl}$ ,  $-\text{NRS}(\text{O})_2\text{-aryl}$ ,  $-\text{NRS}(\text{O})_2\text{-substituted aryl}$ ,  $-\text{NRS}(\text{O})_2\text{-heteroaryl}$ ,  $-\text{NRS}(\text{O})_2\text{-substituted heteroaryl}$ ,  $-\text{NRS}(\text{O})_2\text{-heterocyclic}$ ,  $-\text{NRS}(\text{O})_2\text{-substituted heterocyclic}$ ,  $-\text{NRS}(\text{O})_2\text{-NR-alkyl}$ ,  $-\text{NRS}(\text{O})_2\text{-NR-substituted alkyl}$ ,  $-\text{NRS}(\text{O})_2\text{-NR-aryl}$ ,  $-\text{NRS}(\text{O})_2\text{-NR-substituted aryl}$ ,  $-\text{NRS}(\text{O})_2\text{-NR-heteroaryl}$ ,  $-\text{NRS}(\text{O})_2\text{-NR-substituted heteroaryl}$ ,  $-\text{NRS}(\text{O})_2\text{-NR-heterocyclic}$ ,  $-\text{NRS}(\text{O})_2\text{-NR-substituted heterocyclic}$  where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkyl/substituted alkyl groups substituted with  $-\text{SO}_2\text{-alkyl}$ ,  $-\text{SO}_2\text{-substituted alkyl}$ ,  $-\text{SO}_2\text{-alkenyl}$ ,  $-\text{SO}_2\text{-substituted alkenyl}$ ,  $-\text{SO}_2\text{-cycloalkyl}$ ,  $-\text{SO}_2\text{-substituted cycloalkyl}$ ,  $-\text{SO}_2\text{-aryl}$ ,  $-\text{SO}_2\text{-substituted aryl}$ ,  $-\text{SO}_2\text{-heteroaryl}$ ,  $-\text{SO}_2\text{-substituted heteroaryl}$ ,  $-\text{SO}_2\text{-heterocyclic}$ ,  $-\text{SO}_2\text{-substituted heterocyclic}$  and  $-\text{SO}_2\text{NRR}$  where R is hydrogen or alkyl.

"Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

"Substituted alkoxy" refers to the group "substituted alkyl-O-".

5 "Alkenoxy" refers to the group "alkenyl-O".

"Substituted alkenoxy" refers to the group "substituted alkenyl-O".

10 "Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O), heterocyclic-C(O)-, and substituted heterocyclic-C(O)- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

20 "Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

30 "Thiocarbonylamino" refers to the group -C(S)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each

5 R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

10 "Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

20 "Oxysulfonyl" refers to the groups alkyl-SO<sub>2</sub>O-, substituted alkyl-SO<sub>2</sub>O-, alkenyl-SO<sub>2</sub>O-, substituted alkenyl-SO<sub>2</sub>O-, alkynyl-SO<sub>2</sub>O-, substituted alkynyl-SO<sub>2</sub>O-, aryl-SO<sub>2</sub>O-, substituted aryl-SO<sub>2</sub>O-, cycloalkyl-SO<sub>2</sub>O-, substituted cycloalkyl-SO<sub>2</sub>O-, heteroaryl-SO<sub>2</sub>O-, substituted heteroaryl-SO<sub>2</sub>O-, heterocyclic-SO<sub>2</sub>O-, and substituted heterocyclic-SO<sub>2</sub>O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

30 "Alkenyl" refers to alkenyl group preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation.

5 "Substituted alkenyl" refers to alkenyl groups having from 1 to 5  
substituents selected from the group consisting of alkoxy, substituted alkoxy,  
acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino,  
thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino,  
aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy,  
10 aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro,  
carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl,  
carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,  
carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,  
carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl,  
15 guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl,  
substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl,  
substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic,  
heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic,  
cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted  
20 heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,  
oxycarbonylamino, oxythiocarbonylamino, -OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-  
substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-substituted aryl, -OS(O)<sub>2</sub>-heteroaryl,  
-OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-heterocyclic, -OS(O)<sub>2</sub>-substituted  
heterocyclic, -OSO<sub>2</sub>-NRR where R is hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl, -  
25 NRS(O)<sub>2</sub>-substituted alkyl, -NRS(O)<sub>2</sub>-aryl, -NRS(O)<sub>2</sub>-substituted aryl, -  
NRS(O)<sub>2</sub>-heteroaryl, -NRS(O)<sub>2</sub>-substituted heteroaryl, -NRS(O)<sub>2</sub>-heterocyclic,  
-NRS(O)<sub>2</sub>-substituted heterocyclic, -NRS(O)<sub>2</sub>-NR-alkyl, -NRS(O)<sub>2</sub>-NR-  
substituted alkyl, -NRS(O)<sub>2</sub>-NR-aryl, -NRS(O)<sub>2</sub>-NR-substituted aryl, -  
NRS(O)<sub>2</sub>-NR-heteroaryl, -NRS(O)<sub>2</sub>-NR-substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-  
30 heterocyclic, -NRS(O)<sub>2</sub>-NR-substituted heterocyclic where R is hydrogen or  
alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino,  
mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-  
heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-  
heterocyclic amino, mono- and di-substituted heterocyclic amino,

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5 unsymmetric di-substituted amines having different substituents selected from  
alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted  
heteroaryl, heterocyclic and substituted heterocyclic and substituted alkenyl  
groups having amino groups blocked by conventional blocking groups such as  
Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups  
10 substituted with -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-alkenyl, -SO<sub>2</sub>-  
substituted alkenyl, -SO<sub>2</sub>-cycloalkyl, -SO<sub>2</sub>-substituted cycloalkyl, -SO<sub>2</sub>-aryl, -  
SO<sub>2</sub>-substituted aryl, -SO<sub>2</sub>-heteroaryl, -SO<sub>2</sub>-substituted heteroaryl, -SO<sub>2</sub>-  
heterocyclic, -SO<sub>2</sub>-substituted heterocyclic and -SO<sub>2</sub>NRR where R is  
hydrogen or alkyl.

15 "Alkynyl" refers to alkynyl group preferably having from 2 to 10  
carbon atoms and more preferably 3 to 6 carbon atoms and having at least 1  
and preferably from 1-2 sites of alkynyl unsaturation.

20 "Substituted alkynyl" refers to alkynyl groups having from 1 to 5  
substituents selected from the group consisting of alkoxy, substituted alkoxy,  
acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino,  
thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino,  
aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy,  
25 aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro,  
carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl,  
carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,  
carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,  
carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl,  
30 guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl,  
substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl,  
substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic,  
heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic,  
cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted

5 heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,  
oxycarbonylamino, oxythiocarbonylamino, -OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-  
substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-substituted aryl, -OS(O)<sub>2</sub>-heteroaryl,  
-OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-heterocyclic, -OS(O)<sub>2</sub>-substituted  
heterocyclic, -OSO<sub>2</sub>-NRR where R is hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl,  
10 -NRS(O)<sub>2</sub>-substituted alkyl, -NRS(O)<sub>2</sub>-aryl, -NRS(O)<sub>2</sub>-substituted aryl,  
-NRS(O)<sub>2</sub>-heteroaryl, -NRS(O)<sub>2</sub>-substituted heteroaryl, -NRS(O)<sub>2</sub>-  
heterocyclic, -NRS(O)<sub>2</sub>-substituted heterocyclic, -NRS(O)<sub>2</sub>-NR-alkyl,  
-NRS(O)<sub>2</sub>-NR-substituted alkyl, -NRS(O)<sub>2</sub>-NR-aryl,  
-NRS(O)<sub>2</sub>-NR-substituted aryl, -NRS(O)<sub>2</sub>-NR-heteroaryl, -NRS(O)<sub>2</sub>-NR-  
15 substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-heterocyclic, -NRS(O)<sub>2</sub>-NR-substituted  
heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono-  
and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-  
substituted arylamino, mono- and di-heteroarylamino, mono- and di-  
substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-  
20 substituted heterocyclic amino, unsymmetric di-substituted amines having  
different substituents selected from alkyl, substituted alkyl, aryl, substituted  
aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted  
heterocyclic and substituted alkynyl groups having amino groups blocked by  
conventional blocking groups such as Boc, Cbz, formyl, and the like or  
25 alkynyl/substituted alkynyl groups substituted with -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-  
substituted alkyl, -SO<sub>2</sub>-alkenyl, -SO<sub>2</sub>-substituted alkenyl, -SO<sub>2</sub>-cycloalkyl,  
-SO<sub>2</sub>-substituted cycloalkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-substituted aryl, -SO<sub>2</sub>-heteroaryl,  
-SO<sub>2</sub>-substituted heteroaryl, -SO<sub>2</sub>-heterocyclic, -SO<sub>2</sub>-substituted heterocyclic  
and -SO<sub>2</sub>NRR where R is hydrogen or alkyl.

30

"Amidino" refers to the group H<sub>2</sub>NC(=NH)- and the term  
"alkylamidino" refers to compounds having 1 to 3 alkyl groups (e.g.,  
alkylHNC(=NH)-).



5 "Thioamidino" refers to the group  $\text{RSC}(=\text{NH})-$  where R is hydrogen or alkyl.

"Amino" refers to the group  $-\text{NH}_2$ .

10 "Substituted amino" refers to the group  $-\text{NRR}$ , where each R group is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic,  $-\text{SO}_2$ -alkyl,  $-\text{SO}_2$ -substituted alkyl,  $-\text{SO}_2$ -alkenyl,  $-\text{SO}_2$ -substituted alkenyl,  $-\text{SO}_2$ -cycloalkyl,  $-\text{SO}_2$ -substituted cycloalkyl,  $-\text{SO}_2$ -aryl,  $-\text{SO}_2$ -substituted aryl,  $-\text{SO}_2$ -heteroaryl,  $-\text{SO}_2$ -substituted heteroaryl,  $-\text{SO}_2$ -heterocyclic,  $-\text{SO}_2$ -substituted heterocyclic, provided that both R groups are not hydrogen; or the R groups can be joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring.

20 "Aminoacyl" refers to the groups  $-\text{NRC}(\text{O})\text{alkyl}$ ,  $-\text{NRC}(\text{O})\text{substituted alkyl}$ ,  $-\text{NRC}(\text{O})\text{cycloalkyl}$ ,  $-\text{NRC}(\text{O})\text{substituted cycloalkyl}$ ,  $-\text{NRC}(\text{O})\text{alkenyl}$ ,  $-\text{NRC}(\text{O})\text{substituted alkenyl}$ ,  $-\text{NRC}(\text{O})\text{alkynyl}$ ,  $-\text{NRC}(\text{O})\text{substituted alkynyl}$ ,  $-\text{NRC}(\text{O})\text{aryl}$ ,  $-\text{NRC}(\text{O})\text{substituted aryl}$ ,  $-\text{NRC}(\text{O})\text{heteroaryl}$ ,  $-\text{NRC}(\text{O})\text{substituted heteroaryl}$ ,  $-\text{NRC}(\text{O})\text{heterocyclic}$ , and  $-\text{NRC}(\text{O})\text{substituted heterocyclic}$  where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

30 "Aminosulfonyl" refers to the groups  $-\text{NRSO}_2\text{alkyl}$ ,  $-\text{NRSO}_2\text{substituted alkyl}$ ,  $-\text{NRSO}_2\text{cycloalkyl}$ ,  $-\text{NRSO}_2\text{substituted cycloalkyl}$ ,

5 -NRSO<sub>2</sub>alkenyl, -NRSO<sub>2</sub>substituted alkenyl, -NRSO<sub>2</sub>alkynyl,  
-NRSO<sub>2</sub>substituted alkynyl, -NRSO<sub>2</sub>aryl, -NRSO<sub>2</sub>substituted aryl,  
-NRSO<sub>2</sub>heteroaryl, -NRSO<sub>2</sub>substituted heteroaryl, -NRSO<sub>2</sub>heterocyclic, and  
-NRSO<sub>2</sub>substituted heterocyclic where R is hydrogen or alkyl and wherein  
10 alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted  
alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl,  
substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined  
herein.

"Aminocarbonyloxy" refers to the groups -NRC(O)O-alkyl,  
15 -NRC(O)O-substituted alkyl, -NRC(O)O-alkenyl, -NRC(O)O-substituted  
alkenyl, -NRC(O)O-alkynyl, -NRC(O)O-substituted alkynyl, -NRC(O)O-  
cycloalkyl, -NRC(O)O-substituted cycloalkyl, -NRC(O)O-aryl, -NRC(O)O-  
substituted aryl, -NRC(O)O-heteroaryl, -NRC(O)O-substituted heteroaryl,  
-NRC(O)O-heterocyclic, and -NRC(O)O-substituted heterocyclic where R is  
20 hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted  
alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl,  
substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and  
substituted heterocyclic are as defined herein.

25 "Aminosulfonyloxy" refers to the groups -NRSO<sub>2</sub>O-alkyl,  
-NRSO<sub>2</sub>O-substituted alkyl, -NRSO<sub>2</sub>O-alkenyl, -NRSO<sub>2</sub>O-substituted alkenyl,  
-NRSO<sub>2</sub>O-alkynyl, -NRSO<sub>2</sub>O-substituted alkynyl, -NRSO<sub>2</sub>O-cycloalkyl,  
-NRSO<sub>2</sub>O-substituted cycloalkyl, -NRSO<sub>2</sub>O-aryl, -NRSO<sub>2</sub>O-substituted aryl,  
-NRSO<sub>2</sub>O-heteroaryl, -NRSO<sub>2</sub>O-substituted heteroaryl,  
30 -NRSO<sub>2</sub>O-heterocyclic, and -NRSO<sub>2</sub>O-substituted heterocyclic where R is  
hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted  
alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl,  
substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and  
substituted heterocyclic are as defined herein.

5 "Oxycarbonylamino" refers to the groups -OC(O)NH<sub>2</sub>, -OC(O)NRR,  
-OC(O)NR-alkyl, -OC(O)NR-substituted alkyl, -OC(O)NR-alkenyl,  
-OC(O)NR-substituted alkenyl, -OC(O)NR-alkynyl, -OC(O)NR-substituted  
alkynyl, -OC(O)NR-cycloalkyl, -OC(O)NR-substituted cycloalkyl,  
-OC(O)NR-aryl, -OC(O)NR-substituted aryl, -OC(O)NR-heteroaryl,  
10 -OC(O)NR-substituted heteroaryl, -OC(O)NR-heterocyclic, and  
-OC(O)NR-substituted heterocyclic where R is hydrogen, alkyl or where each  
R is joined to form, together with the nitrogen atom a heterocyclic or  
substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl,  
substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted  
15 cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,  
heterocyclic and substituted heterocyclic are as defined herein.

"Oxythiocarbonylamino" refers to the groups -OC(S)NH<sub>2</sub>,  
-OC(S)NRR, -OC(S)NR-alkyl, -OC(S)NR-substituted alkyl, -OC(S)NR-  
20 alkenyl, -OC(S)NR-substituted alkenyl, -OC(S)NR-alkynyl, -OC(S)NR-  
substituted alkynyl, -OC(S)NR-cycloalkyl, -OC(S)NR-substituted cycloalkyl,  
-OC(S)NR-aryl, -OC(S)NR-substituted aryl, -OC(S)NR-heteroaryl,  
-OC(S)NR-substituted heteroaryl, -OC(S)NR-heterocyclic, and  
-OC(S)NR-substituted heterocyclic where R is hydrogen, alkyl or where each  
25 R is joined to form together with the nitrogen atom a heterocyclic or  
substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl,  
substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted  
cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,  
heterocyclic and substituted heterocyclic are as defined herein.

30 "Oxysulfonylamino" refers to the groups -OSO<sub>2</sub>NH<sub>2</sub>, -OSO<sub>2</sub>NRR,  
-OSO<sub>2</sub>NR-alkyl, -OSO<sub>2</sub>NR-substituted alkyl, -OSO<sub>2</sub>NR-alkenyl,  
-OSO<sub>2</sub>NR-substituted alkenyl, -OSO<sub>2</sub>NR-alkynyl, -OSO<sub>2</sub>NR-substituted  
alkynyl, -OSO<sub>2</sub>NR-cycloalkyl, -OSO<sub>2</sub>NR-substituted cycloalkyl,

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5 -OSO<sub>2</sub>NR-aryl, -OSO<sub>2</sub>NR-substituted aryl, -OSO<sub>2</sub>NR-heteroaryl,  
-OSO<sub>2</sub>NR-substituted heteroaryl, -OSO<sub>2</sub>NR-heterocyclic, and  
-OSO<sub>2</sub>NR-substituted heterocyclic where R is hydrogen, alkyl or where each  
R is joined to form, together with the nitrogen atom a heterocyclic or  
substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl,  
10 substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted  
cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,  
heterocyclic and substituted heterocyclic are as defined herein.

15 "Aminocarbonylamino" refers to the groups -NRC(O)NRR,  
-NRC(O)NR-alkyl, -NRC(O)NR-substituted alkyl, -NRC(O)NR-alkenyl,  
-NRC(O)NR-substituted alkenyl, -NRC(O)NR-alkynyl,  
-NRC(O)NR-substituted alkynyl, -NRC(O)NR-aryl, -NRC(O)NR-substituted  
aryl, -NRC(O)NR-cycloalkyl, -NRC(O)NR-substituted cycloalkyl,  
-NRC(O)NR-heteroaryl, and -NRC(O)NR-substituted heteroaryl,  
20 -NRC(O)NR-heterocyclic, and -NRC(O)NR-substituted heterocyclic where  
each R is independently hydrogen, alkyl or where each R is joined to form  
together with the nitrogen atom a heterocyclic or substituted heterocyclic ring  
as well as where one of the amino groups is blocked by conventional blocking  
groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted  
25 alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,  
substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted  
heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

30 "Aminothiocabonylamino" refers to the groups -NRC(S)NRR,  
-NRC(S)NR-alkyl, -NRC(S)NR-substituted alkyl, -NRC(S)NR-alkenyl,  
-NRC(S)NR-substituted alkenyl, -NRC(S)NR-alkynyl, -NRC(S)NR-  
substituted alkynyl, -NRC(S)NR-aryl, -NRC(S)NR-substituted aryl,  
-NRC(S)NR-cycloalkyl, -NRC(S)NR-substituted cycloalkyl, -NRC(S)NR-  
heteroaryl, and -NRC(S)NR-substituted heteroaryl, -NRC(S)NR-heterocyclic,

5 and -NRC(S)NR-substituted heterocyclic where each R is independently  
hydrogen, alkyl or where each R is joined to form together with the nitrogen  
atom a heterocyclic or substituted heterocyclic ring as well as where one of  
the amino groups is blocked by conventional blocking groups such as Boc,  
Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl,  
10 substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted  
cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,  
heterocyclic and substituted heterocyclic are as defined herein.

15 "Aminosulfonylamino" refers to the groups -NRSO<sub>2</sub>NRR,  
-NRSO<sub>2</sub>NR-alkyl, -NRSO<sub>2</sub>NR-substituted alkyl, -NRSO<sub>2</sub>NR-alkenyl,  
-NRSO<sub>2</sub>NR-substituted alkenyl, -NRSO<sub>2</sub>NR-alkynyl,  
-NRSO<sub>2</sub>NR-substituted alkynyl, -NRSO<sub>2</sub>NR-aryl, -NRSO<sub>2</sub>NR-substituted  
aryl, -NRSO<sub>2</sub>NR-cycloalkyl, -NRSO<sub>2</sub>NR-substituted cycloalkyl,  
-NRSO<sub>2</sub>NR-heteroaryl, and -NRSO<sub>2</sub>NR-substituted heteroaryl,  
20 -NRSO<sub>2</sub>NR-heterocyclic, and -NRSO<sub>2</sub>NR-substituted heterocyclic, where  
each R is independently hydrogen, alkyl or where each R is joined to form  
together with the nitrogen atom a heterocyclic or substituted heterocyclic ring  
as well as where one of the amino groups is blocked by conventional blocking  
groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted  
25 alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,  
substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted  
heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

30 "Aryl" or "Ar" refers to an unsaturated aromatic carbocyclic group of  
from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple  
condensed rings (e.g., naphthyl or anthryl) which condensed rings may or  
may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-  
7yl, and the like). Preferred aryls include phenyl and naphthyl.

5                   Substituted aryl refers to aryl groups which are substituted with from  
1 to 3 substituents selected from the group consisting of hydroxy, acyl,  
acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy,  
substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl,  
amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy,  
10           aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl,  
aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy,  
heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted  
heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl,  
carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-  
15           substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl,  
carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido,  
cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl,  
thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted  
thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl,  
20           substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl,  
substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy,  
substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy,  
heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino,  
oxythiocarbonylamino, -S(O)<sub>2</sub>-alkyl, -S(O)<sub>2</sub>-substituted alkyl, -S(O)<sub>2</sub>-  
25           cycloalkyl, -S(O)<sub>2</sub>-substituted cycloalkyl, -S(O)<sub>2</sub>-alkenyl, -S(O)<sub>2</sub>-substituted  
alkenyl, -S(O)<sub>2</sub>-aryl, -S(O)<sub>2</sub>-substituted aryl, -S(O)<sub>2</sub>-heteroaryl, -S(O)<sub>2</sub>-  
substituted heteroaryl, -S(O)<sub>2</sub>-heterocyclic, -S(O)<sub>2</sub>-substituted heterocyclic,  
-OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-substituted  
aryl, -OS(O)<sub>2</sub>-heteroaryl, -OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-  
30           heterocyclic, -OS(O)<sub>2</sub>-substituted heterocyclic, -OSO<sub>2</sub>-NRR where R is  
hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl, -NRS(O)<sub>2</sub>-substituted alkyl, -NRS(O)<sub>2</sub>-  
aryl, -NRS(O)<sub>2</sub>-substituted aryl, -NRS(O)<sub>2</sub>-heteroaryl, -NRS(O)<sub>2</sub>-substituted  
heteroaryl, -NRS(O)<sub>2</sub>-heterocyclic, -NRS(O)<sub>2</sub>-substituted heterocyclic,  
-NRS(O)<sub>2</sub>-NR-alkyl, -NRS(O)<sub>2</sub>-NR-substituted alkyl, -NRS(O)<sub>2</sub>-NR-aryl,

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5 -NRS(O)<sub>2</sub>-NR-substituted aryl, -NRS(O)<sub>2</sub>-NR-heteroaryl, -NRS(O)<sub>2</sub>-NR-substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-heterocyclic, -NRS(O)<sub>2</sub>-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO<sub>2</sub>NRR where R is hydrogen or alkyl.

"Aryloxy" refers to the group aryl-O- which includes, by way of example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Aryloxyaryl" refers to the group -aryl-O-aryl.

25 "Substituted aryloxyaryl" refers to aryloxyaryl groups substituted with from 1 to 3 substituents on either or both aryl rings selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-

5 substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,  
carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,  
carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl,  
substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted  
thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic,  
10 substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino,  
guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic,  
substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,  
substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,  
oxycarbonylamino, oxythiocarbonylamino, -S(O)<sub>2</sub>-alkyl, -S(O)<sub>2</sub>-substituted  
15 alkyl, -S(O)<sub>2</sub>-cycloalkyl, -S(O)<sub>2</sub>-substituted cycloalkyl, -S(O)<sub>2</sub>-alkenyl, -S(O)<sub>2</sub>-  
substituted alkenyl, -S(O)<sub>2</sub>-aryl, -S(O)<sub>2</sub>-substituted aryl, -S(O)<sub>2</sub>-heteroaryl, -  
S(O)<sub>2</sub>-substituted heteroaryl, -S(O)<sub>2</sub>-heterocyclic, -S(O)<sub>2</sub>-substituted  
heterocyclic, -OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-  
substituted aryl, -OS(O)<sub>2</sub>-heteroaryl, -OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-  
20 heterocyclic, -OS(O)<sub>2</sub>-substituted heterocyclic, -OSO<sub>2</sub>-NRR where R is  
hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl, -NRS(O)<sub>2</sub>-substituted alkyl, -NRS(O)<sub>2</sub>-  
aryl, -NRS(O)<sub>2</sub>-substituted aryl, -NRS(O)<sub>2</sub>-heteroaryl, -NRS(O)<sub>2</sub>-substituted  
heteroaryl, -NRS(O)<sub>2</sub>-heterocyclic, -NRS(O)<sub>2</sub>-substituted heterocyclic, -  
NRS(O)<sub>2</sub>-NR-alkyl, -NRS(O)<sub>2</sub>-NR-substituted alkyl, -NRS(O)<sub>2</sub>-NR-aryl, -  
25 NRS(O)<sub>2</sub>-NR-substituted aryl, -NRS(O)<sub>2</sub>-NR-heteroaryl, -NRS(O)<sub>2</sub>-NR-  
substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-heterocyclic, -NRS(O)<sub>2</sub>-NR-substituted  
heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono-  
and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-  
substituted arylamino, mono- and di-heteroarylamino, mono- and di-  
30 substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-  
substituted heterocyclic amino, unsymmetric di-substituted amines having  
different substituents selected from alkyl, substituted alkyl, aryl, substituted  
aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted  
heterocyclic and amino groups on the substituted aryl blocked by conventional

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5 blocking groups such as Boc, Cbz, formyl, and the like or substituted with -  
SO<sub>2</sub>NRR where R is hydrogen or alkyl.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 8 carbon atoms  
having a single cyclic ring including, by way of example, cyclopropyl,  
10 cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and the like. Excluded from  
this definition are multi-ring alkyl groups such as adamantanyl, etc.

"Cycloalkenyl" refers to cyclic alkenyl groups of from 3 to 8 carbon  
atoms having single or multiple unsaturation but which are not aromatic.

15 "Substituted cycloalkyl" and "substituted cycloalkenyl" refer to a  
cycloalkyl and cycloalkenyl groups, preferably of from 3 to 8 carbon atoms,  
having from 1 to 5 substituents selected from the group consisting of oxo  
(=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino,  
20 thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino,  
aminoacyl, aminocarbonylamino, aminothiocarbonylamino,  
aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy,  
aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro,  
carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl,  
25 carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,  
carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,  
carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl,  
guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl,  
substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl,  
30 substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic,  
heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic,  
cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted  
heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,  
oxycarbonylamino, oxythiocarbonylamino, -OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-

5 substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-substituted aryl, -OS(O)<sub>2</sub>-heteroaryl,  
-OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-heterocyclic, -OS(O)<sub>2</sub>-substituted  
heterocyclic, -OSO<sub>2</sub>-NRR where R is hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl,  
-NRS(O)<sub>2</sub>-substituted alkyl, -NRS(O)<sub>2</sub>-aryl, -NRS(O)<sub>2</sub>-substituted aryl,  
-NRS(O)<sub>2</sub>-heteroaryl, -NRS(O)<sub>2</sub>-substituted heteroaryl,  
10 -NRS(O)<sub>2</sub>-heterocyclic, -NRS(O)<sub>2</sub>-substituted heterocyclic,  
-NRS(O)<sub>2</sub>-NR-alkyl, -NRS(O)<sub>2</sub>-NR-substituted alkyl, -NRS(O)<sub>2</sub>-NR-aryl,  
-NRS(O)<sub>2</sub>-NR-substituted aryl, -NRS(O)<sub>2</sub>-NR-heteroaryl, -NRS(O)<sub>2</sub>-NR-  
substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-heterocyclic, -NRS(O)<sub>2</sub>-NR-substituted  
heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono-  
15 and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-  
substituted arylamino, mono- and di-heteroarylamino, mono- and di-  
substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-  
substituted heterocyclic amino, unsymmetric di-substituted amines having  
different substituents selected from alkyl, substituted alkyl, aryl, substituted  
20 aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted  
heterocyclic and substituted alkynyl groups having amino groups blocked by  
conventional blocking groups such as Boc, Cbz, formyl, and the like or  
alkynyl/substituted alkynyl groups substituted with -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-  
substituted alkyl, -SO<sub>2</sub>-alkenyl, -SO<sub>2</sub>-substituted alkenyl, -SO<sub>2</sub>-cycloalkyl,  
25 -SO<sub>2</sub>-substituted cycloalkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-substituted aryl, -SO<sub>2</sub>-heteroaryl,  
-SO<sub>2</sub>-substituted heteroaryl, -SO<sub>2</sub>-heterocyclic, -SO<sub>2</sub>-substituted heterocyclic  
and -SO<sub>2</sub>NRR where R is hydrogen or alkyl.

"Cycloalkoxy" refers to -O-cycloalkyl groups.

"Substituted cycloalkoxy" refers to -O-substituted cycloalkyl groups.

"Cycloalkenoxy" refers to -O-cycloalkenyl groups.

5 "Substituted cycloalkenoxy" refers to -O-substituted cycloalkenyl groups.

"Guanidino" refers to the groups -NRC(=NR)NRR,  
-NRC(=NR)NR-alkyl, -NRC(=NR)NR-substituted alkyl, -NRC(=NR)NR-  
10 alkenyl, -NRC(=NR)NR-substituted alkenyl, -NRC(=NR)NR-alkynyl,  
-NRC(=NR)NR-substituted alkynyl, -NRC(=NR)NR-aryl,  
-NRC(=NR)NR-substituted aryl, -NRC(=NR)NR-cycloalkyl,  
-NRC(=NR)NR-heteroaryl, -NRC(=NR)NR-substituted heteroaryl,  
-NRC(=NR)NR-heterocyclic, and -NRC(=NR)NR-substituted heterocyclic  
15 where each R is independently hydrogen and alkyl as well as where one of the  
amino groups is blocked by conventional blocking groups such as Boc, Cbz,  
formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted  
alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl,  
substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and  
20 substituted heterocyclic are as defined herein.

"Guanidinosulfone" refers to the groups -NRC(=NR)NRSO<sub>2</sub>-alkyl,  
-NRC(=NR)NRSO<sub>2</sub>-substituted alkyl, -NRC(=NR)NRSO<sub>2</sub>-alkenyl,  
-NRC(=NR)NRSO<sub>2</sub>-substituted alkenyl, -NRC(=NR)NRSO<sub>2</sub>-alkynyl,  
25 -NRC(=NR)NRSO<sub>2</sub>-substituted alkynyl, -NRC(=NR)NRSO<sub>2</sub>-aryl,  
-NRC(=NR)NRSO<sub>2</sub>-substituted aryl, -NRC(=NR)NRSO<sub>2</sub>-cycloalkyl,  
-NRC(=NR)NRSO<sub>2</sub>-substituted cycloalkyl, -NRC(=NR)NRSO<sub>2</sub>-heteroaryl,  
and -NRC(=NR)NRSO<sub>2</sub>-substituted heteroaryl, -NRC(=NR)NRSO<sub>2</sub>-  
heterocyclic, and -NRC(=NR)NRSO<sub>2</sub>-substituted heterocyclic where each R  
30 is independently hydrogen and alkyl and wherein alkyl, substituted alkyl,  
alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,  
substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted  
heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

5           "Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is either chloro or bromo.

10           "Heteroaryl" refers to an aromatic carbocyclic group of from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within the ring or oxides thereof. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indoliziny1 or benzothieryl). Additionally, the heteroatoms of the heteroaryl group may be oxidized, i.e., to form pyridine N-oxides or 1,1-dioxo-1,2,5-thiadiazoles and the like. Preferred heteroaryls include pyridyl, pyrrolyl, 15 indolyl, furyl, pyridaziny1, pyrimidiny1, pyraziny1, 1-oxo-1,2,5-thiadiazolyl and 1,1-dioxo-1,2,5-thiadiazolyl. The term "heteroaryl having two nitrogen atoms in the heteroaryl ring" refers to a heteroaryl group having two, and only two, nitrogen atoms in the heteroaryl ring and optionally containing 1 or 2 other heteroatoms in the heteroaryl ring, such as oxygen or sulfur

20           "Substituted heteroaryl" refers to heteroaryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, 25 substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocabonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, 30 carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted

5 thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl,  
substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl,  
substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy,  
substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy,  
heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino,  
10 oxythiocarbonylamino, -S(O)<sub>2</sub>-alkyl, -S(O)<sub>2</sub>-substituted alkyl, -S(O)<sub>2</sub>-  
cycloalkyl, -S(O)<sub>2</sub>-substituted cycloalkyl, -S(O)<sub>2</sub>-alkenyl, -S(O)<sub>2</sub>-substituted  
alkenyl, -S(O)<sub>2</sub>-aryl, -S(O)<sub>2</sub>-substituted aryl, -S(O)<sub>2</sub>-heteroaryl, -S(O)<sub>2</sub>-  
substituted heteroaryl, -S(O)<sub>2</sub>-heterocyclic, -S(O)<sub>2</sub>-substituted heterocyclic,  
-OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-substituted  
15 aryl, -OS(O)<sub>2</sub>-heteroaryl, -OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-  
heterocyclic, -OS(O)<sub>2</sub>-substituted heterocyclic, -OSO<sub>2</sub>-NRR where R is  
hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl, -NRS(O)<sub>2</sub>-substituted alkyl, -NRS(O)<sub>2</sub>-  
aryl, -NRS(O)<sub>2</sub>-substituted aryl, -NRS(O)<sub>2</sub>-heteroaryl, -NRS(O)<sub>2</sub>-substituted  
heteroaryl, -NRS(O)<sub>2</sub>-heterocyclic, -NRS(O)<sub>2</sub>-substituted heterocyclic,  
20 -NRS(O)<sub>2</sub>-NR-alkyl, -NRS(O)<sub>2</sub>-NR-substituted alkyl, -NRS(O)<sub>2</sub>-NR-aryl, -  
NRS(O)<sub>2</sub>-NR-substituted aryl, -NRS(O)<sub>2</sub>-NR-heteroaryl, -NRS(O)<sub>2</sub>-NR-  
substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-heterocyclic, -NRS(O)<sub>2</sub>-NR-substituted  
heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono-  
and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-  
25 substituted arylamino, mono- and di-heteroarylamino, mono- and di-  
substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-  
substituted heterocyclic amino, unsymmetric di-substituted amines having  
different substituents selected from alkyl, substituted alkyl, aryl, substituted  
aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted  
30 heterocyclic and amino groups on the substituted aryl blocked by conventional  
blocking groups such as Boc, Cbz, formyl, and the like or substituted with -  
SO<sub>2</sub>NRR where R is hydrogen or alkyl.

"Heteroaryloxy" refers to the group -O-heteroaryl and "substituted heteroaryloxy" refers to the group -O-substituted heteroaryl.

"Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more of the rings can be aryl or heteroaryl.

"Substituted heterocyclic" refers to heterocycle groups which are substituted with from 1 to 3 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)<sub>2</sub>-alkyl, -OS(O)<sub>2</sub>-substituted alkyl, -OS(O)<sub>2</sub>-aryl, -OS(O)<sub>2</sub>-substituted aryl, -OS(O)<sub>2</sub>-heteroaryl, -OS(O)<sub>2</sub>-substituted heteroaryl, -OS(O)<sub>2</sub>-heterocyclic, -OS(O)<sub>2</sub>-substituted heterocyclic, -OSO<sub>2</sub>-NRR where R is hydrogen or alkyl, -NRS(O)<sub>2</sub>-alkyl,

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5 -NRS(O)<sub>2</sub>-substituted alkyl, -NRS(O)<sub>2</sub>-aryl, -NRS(O)<sub>2</sub>-substituted aryl,  
-NRS(O)<sub>2</sub>-heteroaryl, -NRS(O)<sub>2</sub>-substituted heteroaryl,  
-NRS(O)<sub>2</sub>-heterocyclic, -NRS(O)<sub>2</sub>-substituted heterocyclic,  
-NRS(O)<sub>2</sub>-NR-alkyl, -NRS(O)<sub>2</sub>-NR-substituted alkyl, -NRS(O)<sub>2</sub>-NR-aryl,  
-NRS(O)<sub>2</sub>-NR-substituted aryl, -NRS(O)<sub>2</sub>-NR-heteroaryl, -NRS(O)<sub>2</sub>-NR-  
10 substituted heteroaryl, -NRS(O)<sub>2</sub>-NR-heterocyclic, -NRS(O)<sub>2</sub>-NR-substituted  
heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono-  
and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-  
substituted arylamino, mono- and di-heteroarylamino, mono- and di-  
substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-  
15 substituted heterocyclic amino, unsymmetric di-substituted amines having  
different substituents selected from alkyl, substituted alkyl, aryl, substituted  
aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted  
heterocyclic and substituted alkynyl groups having amino groups blocked by  
conventional blocking groups such as Boc, Cbz, formyl, and the like or  
20 alkynyl/substituted alkynyl groups substituted with -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-  
substituted alkyl, -SO<sub>2</sub>-alkenyl, -SO<sub>2</sub>-substituted alkenyl, -SO<sub>2</sub>-cycloalkyl,  
-SO<sub>2</sub>-substituted cycloalkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-substituted aryl, -SO<sub>2</sub>-heteroaryl,  
-SO<sub>2</sub>-substituted heteroaryl, -SO<sub>2</sub>-heterocyclic, -SO<sub>2</sub>-substituted heterocyclic  
and -SO<sub>2</sub>NRR where R is hydrogen or alkyl.

25

Examples of heterocycles and heteroaryls include, but are not limited  
to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine,  
pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine,  
quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine,  
30 quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline,  
phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole,  
phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine,  
piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-  
tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene,

5 benzo[b]thiophene, morpholino, thiomorpholino, piperidiny1, pyrrolidine,  
tetrahydrofuranyl, and the like.

"Heterocyclyoxy" refers to the group -O-heterocyclic and "substituted  
heterocyclyoxy" refers to the group -O-substituted heterocyclic.

10

"Thiol" refers to the group -SH.

"Thioalkyl" or "alkylthio" refers to the groups -S-alkyl

15

"Substituted thioalkyl" refers to the group -S-substituted alkyl.

"Alkylsulfoxy" refers to the group -SO-alkyl.

20

"Substituted alkylsulfoxy" refers to the group -SO-substituted alkyl.

"Alkylsulfonyl" refers to the group -SO<sub>2</sub>-alkyl.

"Substituted alkylsulfonyl" refers to the group -SO<sub>2</sub>-substituted alkyl.

25

"Thiocycloalkyl" refers to the groups -S-cycloalkyl.

"Substituted thiocycloalkyl" refers to the group -S-substituted  
cycloalkyl.

30

"Thioaryl" refers to the group -S-aryl and "substituted thioaryl" refers  
to the group -S-substituted aryl.

"Thioheteroaryl" refers to the group -S-heteroaryl and "substituted  
thioheteroaryl" refers to the group -S-substituted heteroaryl.

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5 "Thioheterocyclic" refers to the group -S-heterocyclic and "substituted thioheterocyclic" refers to the group -S-substituted heterocyclic.

"Alkylamino" or "substituted alkylamino" refers to the group -NHR wherein R is alkyl or substituted alkyl groups respectively as defined above.

10 "Dialkylamino" or "substituted dialkylamino" refers to the group -NRR wherein each R is alkyl or substituted alkyl groups respectively as defined above.

15 "Alkylsulfonylamino" or "substituted alkylsulfonylamino" refers to the group -NHSO<sub>2</sub>R wherein R is alkyl or substituted alkyl groups respectively as defined above.

"N-Alkylsulfonyl-N-alkylamino" refers to the group -NRSO<sub>2</sub>R<sup>a</sup> wherein R and R<sup>a</sup> are independently alkyl wherein alkyl is as defined above.

20 "Substituted N-alkylsulfonyl-N-alkylamino" refers to the group -NRSO<sub>2</sub>R<sup>a</sup> wherein R and R<sup>a</sup> are independently alkyl or substituted alkyl groups wherein substituted alkyl is as defined above.

25 "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of Formula I which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule  
30 contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

5        Compound Preparation

          The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

10           Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

15           Furthermore, the compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

5

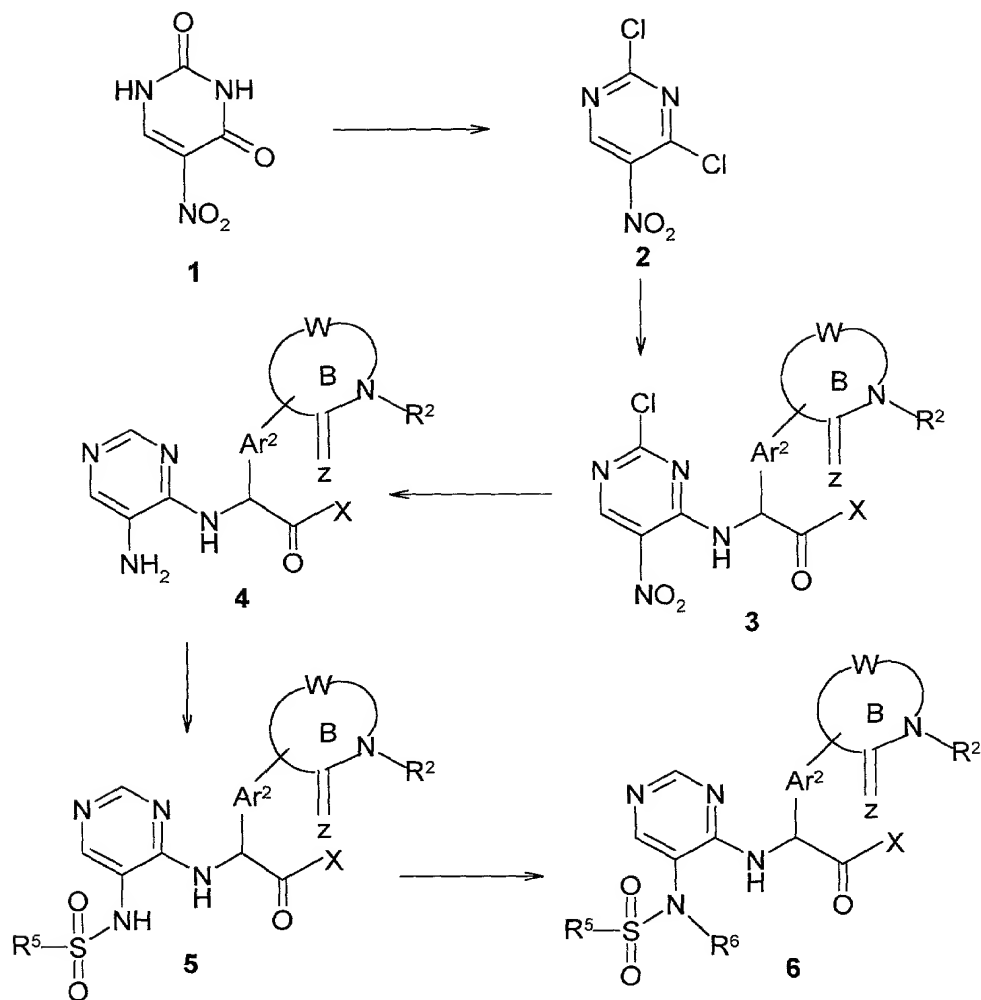


15

25

30

Scheme 1



5

As shown in Scheme 1, 5-nitrouracil, **1**, (commercially available from Aldrich Chemical Company, Milwaukee, Wisconsin USA) is treated with phosphorus oxychloride and *N,N*-dimethylaniline according to the procedure described in Whittaker, *J. Chem. Soc.* **1951**, 1565 to give 1,3-dichloro-4-nitropyrimidine, **2**.

10

1,3-Dichloro-4-nitropyrimidine, **2**, is then reacted with about one molar equivalent of an amino acid derivative of the formula (a) or (b) shown above in the presence of a trialkylamine, such as diisopropylethylamine (DIEA). Typically, this reaction is conducted in an inert diluent, such as dichloromethane, at a temperature ranging from about 0°C to about 10°C for about 5 min. to about 6 hours to afford intermediate **3** where X is -OP<sup>1</sup>.

The nitro group of intermediate **3** is then reduced using a conventional reducing agent, such as hydrogen and a palladium on carbon catalyst. When hydrogen and palladium on carbon are employed as the reducing agent, the chloro group of intermediate **3** is also removed. This reaction is typically conducted by contacting **3** with a Degussa-type palladium on carbon catalyst (typically 20%) and excess sodium bicarbonate in an inert diluent, such as methanol, under hydrogen (typically about 55 psi) for about 12 to 36 hours at ambient temperature to afford amino intermediate **4**.

Amino intermediate **4** is then reacted with a sulfonyl chloride of the formula: R<sup>5</sup>-S(O)<sub>2</sub>-Cl, where R<sup>5</sup> is as defined herein, to provide sulfonamide intermediate **5**. This reaction is typically conducted by reacting the amino intermediate **4** with at least one equivalent, preferably about 1.1 to about 2 equivalents, of the sulfonyl chloride in an inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like, as the base. Upon completion of the reaction, the resulting sulfonamide **5** is recovered by

5 conventional methods including neutralization, extraction, precipitation,  
chromatography, filtration, and the like.

Other heteroaryl intermediates may also be employed in the above  
described reactions including, but not limited to, 2-chloro-3-nitropyrazine (*J.*  
10 *Med. Chem.* **1984**, 27, 1634); 4-chloro-5-nitroimidazole (*J. Chem. Soc.* **1930**,  
268); and the like.

The amino acid derivatives (a) or (b), employed in the above reactions  
can be prepared from known amino acids or by known methods for the  
15 preparation of amino acids. For example, amino acid derivatives (a) or (b)  
where Ar<sup>1</sup> is aryl, specifically phenyl, can be prepared from commercially  
available 4'-iodophenylalanine (Aldrich) as follows. 4'-Iodophenylalanine is  
first converted in two steps to give N-*tert*-butoxycarbonyl-4'-  
iodophenylalanine methyl ester (*see.*, *J. Am. Chem. Soc.* **1992**, 114(19),  
20 7597-7598). The latter compound is then reacted with a suitably substituted  
(trialkylstannyl)-heterocycle (*see.*, *J. Org. Chem.* **1994**, 59(20), 5905-5911)  
or a suitably substituted (dihydroxyboronyl)heterocycle (*see.*, *Tet. Lett.* **1993**,  
34(13), 2127-2130), utilizing a palladium catalyst to form a carbon-carbon  
bond, to give an N-*tert*-butoxycarbonyl-4'-(heterocyclyl)-phenylalanine  
25 methyl ester. (A detailed description of the synthesis of N-*tert*-  
butoxycarbonyl-4-(1-methyl-4-methoxypyridin-2-one-3-yl)-L-phenylalanine  
methyl ester is provided in working examples.) The latter compound can be  
reacted with hydrogen chloride to give the hydrochloride salt of a 4'-  
(heterocyclyl)phenylalanine methyl ester, which would be suitable for use in a  
30 reaction described above.

Alternatively for example, N-*tert*-butoxycarbonyl-4'-  
iodophenylalanine methyl ester can be converted in one step to give either N-  
*tert*-butoxycarbonyl-4'-(trimethylstannyl)phenylalanine methyl ester (*see.*,

5 *Syn. Lett.* **1997**, (7), 1403-1405) or N-*tert*-butoxycarbonyl-4'-  
(pinacolatoborono)phenylalanine methyl ester (*see.*, *Tet. Lett.* **1999**, 40(2),  
213-216). Either of the latter compounds could be reacted with a suitably  
substituted iodoheterocycle or bromoheterocycle, utilizing a palladium  
catalyst to form a carbon-carbon bond, to give an N-*tert*-butoxycarbonyl-4'-  
10 (heterocyclyl)phenylalanine methyl ester (*see.*, *Syn. Lett.* **1997**, (7), 1403-  
1405; *Tetrahedron Lett.* **1999**, 40(2), 213-216). The *tert*-butoxycarbonyl  
group of the latter compound could be removed as described above.  
Alternatively for example, N-*tert*-butoxycarbonyl-4'-iodophenylalanine  
methyl ester could be reacted with a suitably substituted heterocycle featuring  
15 an N-H group, utilizing a copper catalyst to form a carbon-nitrogen bond, to  
give an N-*tert*-butoxycarbonyl-4'-(heterocyclyl)phenylalanine methyl ester  
(*see.*, *J. Med. Chem.* **1998**, 41(13), 2268-2277). The *tert*-butoxycarbonyl  
group of the latter compound could be removed as described above.  
Alternatively, for example, commercially available 4'-nitrophenylalanine  
20 (Aldrich) could be converted in three steps to N-*tert*-butoxycarbonyl-4'-  
aminophenylalanine methyl ester (*see.*, *J. Org. Chem.* **1999**, 64(10), 3467-  
3475). The latter compound could be reacted with an omega-haloalkyl-  
isocyanate to give an N-*tert*-butoxycarbonyl-4'-(omega-  
haloalkylaminocarbonyl)-amino)-phenylalanine methyl ester (*see.*, *Khim.*  
25 *Farm. Zh.* **1984**, 18(12), 1432-1436). The latter compound could be reacted  
with sodium hydride to give an N-*tert*-butoxycarbonyl-4'-(1,3-diaza-2-  
oxalicyclyl)phenylalanine methyl ester (*see.*, *Bioorg. Med. Chem. Lett.*  
**1999**, 9(5), 749-754). The *tert*-butoxycarbonyl group of the latter compound  
could be removed as described above.

30  
For example, amino acid derivatives (a) or (b) where Ar<sup>1</sup> is  
heteroaryl, these can be prepared by methods well known in the art. For  
example, the procedures of Schow et al. (*J. Org. Chem.* **1994**, 59(22), 6850-  
6852) or the procedures of Ye et al. (*J. Org. Chem.* **1995**, 60(8), 2640-2641)

5 or the procedures of Myers et al. (*J. Org. Chem.* **1996**, 61(22), 813-815) may  
be used to prepare 5-hydroxypyridin-2-ylalanine. Using standard procedures,  
the carboxyl group could be protected with a methyl ester, and the amino  
group could be protected with *tert*-butoxycarbonyl group. The procedure of  
Ksander et al. (*J. Med. Chem.* **1995**, 38(10), 1689-1700) could be used to  
10 convert the phenol of such a protected derivative into a triflate. The  
procedure of Firooznia et al. (*Tet. Lett.* **1999**, 40(2), 213-216) could be used  
to convert the triflate into pinacolatoborono derivative. As described above,  
the pinacolatoborono derivative could be applied in a palladium catalyzed  
coupling with a suitably substituted iodoheterocycle or bromoheterocycle.

15 The procedures of Yamano et al. (*Tetrahedron.* **1992**, 48(8), 1457-  
1464) or the procedures of Andrews et al. (*J. Chem. Soc. Perkin Trans. 1.*  
**1995**, 11, 1335-1340) may be used to prepare 2-hydroxypyridin-2-ylalanine.  
Using procedures described above, this could be converted into a protected  
20 pinacolatoborono derivative, which could be applied in a palladium catalyzed  
coupling with a suitably substituted iodoheterocycle or bromoheterocycle.

25 The procedures of Shiotani et al. (*J. Org. Chem.* **1997**, 34(3), 941-  
952) could be used to prepare a pyridin-2-one fused via the 4 and 5 positions  
with a tetrahydrofuran. Following methods described in the working  
examples, this compound could be elaborated into a 1-methyl-3-iodopyridin-  
2-one fused via the 4 and 5 positions with a tetrahydrofuran. As described  
above, this compound could be applied in a palladium catalyzed coupling with  
a suitably protected pinacolatoborono phenylalanine or a suitably protected  
30 pinacolatoborono heteroarylalanine.

The procedures of Adembri (*J. Chem. Soc. Perkin Trans. 1.* **1975**,  
2190-2194) could be used to prepare a pyridin-2-one fused via the 4 and 5  
positions with an isoxazole. Following methods described in the working



5 examples, this compound could be elaborated into a 1-methyl-3-iodopyridin-  
2-one fused via the 4 and 5 positions with an isoxazole. As described above,  
this compound could be applied in a palladium catalyzed coupling with a  
suitably protected pinacolatoborono phenylalanine or a suitably protected  
pinacolatoborono heteroarylalanine.

10 The procedures of Dorofeenko et al. (*Khim. Geterotsikl. Soedin.*  
**1976**, 533) could be used to prepare a pyridin-2-one fused via the 4 and 5  
positions with a furan. Following methods described in the working  
examples, this compound could be elaborated into a 1-methyl-3-iodopyridin-  
15 2-one fused via the 4 and 5 positions with an isoxazole. As described above,  
this compound could be applied in a palladium catalyzed coupling with a  
suitably protected pinacolatoborono phenylalanine or a suitably protected  
pinacolato heteroarylalanine.

20 The sulfonyl chlorides employed in the above reaction are also either  
known compounds or compounds that can be prepared from known  
compounds by conventional synthetic procedures. Such compounds are  
typically prepared from the corresponding sulfonic acid, i.e., from  
compounds of the formula  $R^5-SO_3H$  where  $R^5$  is as defined above, using  
25 phosphorous trichloride and phosphorous pentachloride. This reaction is  
generally conducted by contacting the sulfonic acid with about 2 to 5 molar  
equivalents of phosphorous trichloride and phosphorous pentachloride, either  
neat or in an inert solvent, such as dichloromethane, at temperature in the  
range of about 0°C to about 80°C for about 1 to about 48 hours to afford the  
30 sulfonyl chloride. Alternatively, the sulfonyl chloride can be prepared from  
the corresponding thiol compound, i.e., from compounds of the formula  $R^5-SH$   
where  $R^5$  is as defined herein, by treating the thiol with chlorine ( $Cl_2$ ) and  
water under conventional reaction conditions.

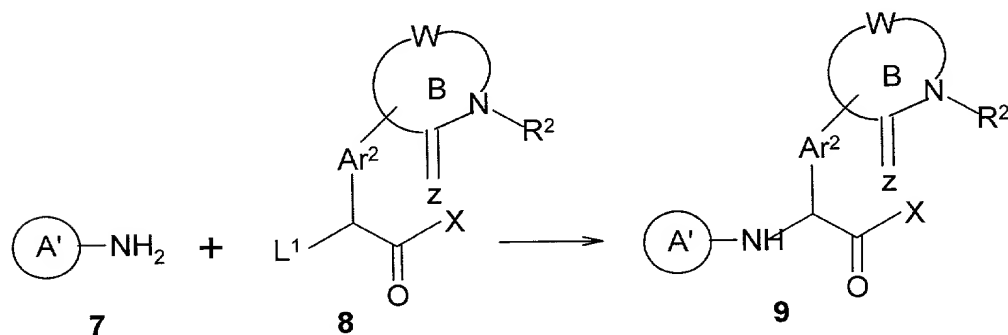
5           Examples of sulfonyl chlorides suitable for use in this invention  
include, but are not limited to, methanesulfonyl chloride, 2-propanesulfonyl  
chloride, 1-butanesulfonyl chloride, benzenesulfonyl chloride, 1-  
naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, *p*-  
toluenesulfonyl chloride,  $\alpha$ -toluenesulfonyl chloride, 4-  
10   acetamidobenzenesulfonyl chloride, 4-amidinobenzenesulfonyl chloride, 4-  
*tert*-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-  
carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-  
dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-  
dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl  
15   chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl  
chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-  
methylamidobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 4-  
thioamidobenzenesulfonyl chloride, 4-trifluoromethylbenzenesulfonyl  
chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-  
20   trimethylbenzenesulfonyl chloride, 2-phenylethanesulfonyl chloride, 2-  
thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-  
dichloro-4-thiophenesulfonyl chloride, 2-thiazolesulfonyl chloride, 2-methyl-  
4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride, 1-methyl-  
4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-pyrazolesulfonyl  
25   chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride and the  
like. If desired, a sulfonyl fluoride, sulfonyl bromide or sulfonic acid  
anhydride may be used in place of the sulfonyl chloride in the above reaction  
to form the sulfonamide intermediate **5**.

30           If desired, sulfonamide intermediate **5** can be alkylated at the  
sulfonamide nitrogen atom to provide compound **6**. For example, **5** can be  
contacted with excess diazomethane (generated, for example, using 1-methyl-  
3-nitro-1-nitrosoguanidine and sodium hydroxide) to afford **6** where R<sup>6</sup> is

methyl. Other conventional alkylation procedures and reagents may also be employed to prepare various compounds of this invention.

In another preferred embodiment, compounds of this invention (Ia) may be prepared by displacement of a leaving group as shown in Scheme 2:

Scheme 2

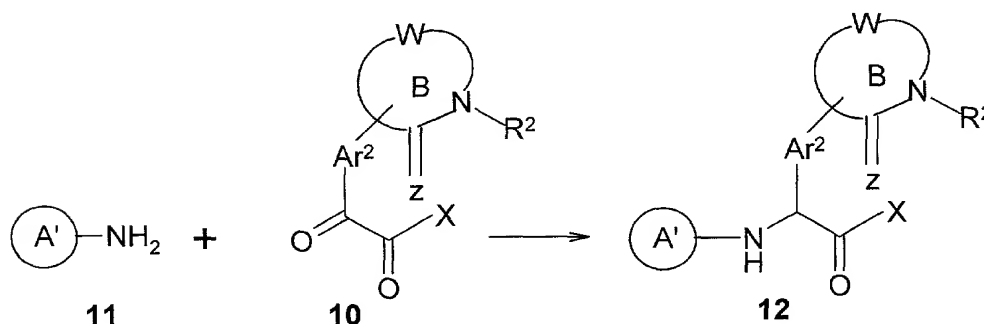


where B, Ar<sup>1</sup>, Ar<sup>2</sup>, and X are as defined herein; A' is heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic containing two nitrogen atoms in the heteroaryl or heterocyclic ring; and L<sup>1</sup> is a leaving group, such as chloro, bromo, iodo, sulfonate ester and the like.

Typically, this reaction is conducted by combining approximately stoichiometric equivalents of 7 and 8 in a suitable inert diluent such as water, dimethylsulfoxide (DMSO) and the like, with an excess of a suitable base such as sodium bicarbonate, sodium hydroxide, etc. to scavenge the acid generated by the reaction. The reaction is preferably conducted at from about 25°C to about 100°C until reaction completion which typically occurs within 1 to about 24 hours. This reaction is further described in U.S. Patent No. 3,598,859, which is incorporated herein by reference in its entirety. Upon reaction completion, the product 9 is recovered by conventional methods including precipitation, chromatography, filtration and the like.

In still another alternative embodiment, compounds of this invention can be prepared by reductive amination of a suitable 2-oxocarboxylic acid ester, **10**, such as a pyruvate ester, as shown in Scheme 3:

Scheme 3

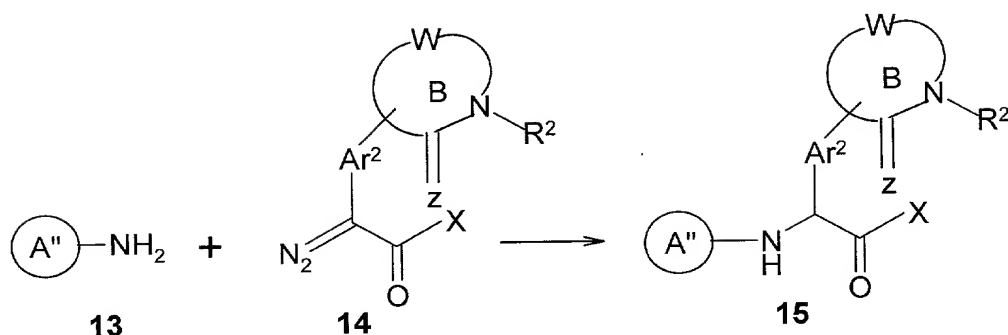


where B, Ar<sup>1</sup>, Ar<sup>2</sup>, and X are as defined herein.

Generally, this reaction is conducted by combining equimolar amounts of **10** and **11** in an inert diluent such as methanol, ethanol and the like under conditions which provide for imine formation (not shown). The imine formed is then reduced under conventional conditions by a suitable reducing agent such as sodium cyanoborohydride, H<sub>2</sub>/palladium on carbon and the like to form the product **12**. In a particularly preferred embodiment, the reducing agent is H<sub>2</sub>/palladium on carbon which is incorporated into the initial reaction medium thereby permitting imine reduction *in situ* in a one pot procedure to provide **12**. The reaction is preferably conducted at from about 20°C to about 80°C at a pressure of from 1 to 10 atmospheres until reaction completion which typically occurs within 1 to about 24 hours. Upon reaction completion, the product **12** is recovered by conventional methods including chromatography, filtration and the like.

Alternatively, certain compounds of this invention can be prepared via a rhodium-catalyzed insertion reaction as shown in Scheme 4:

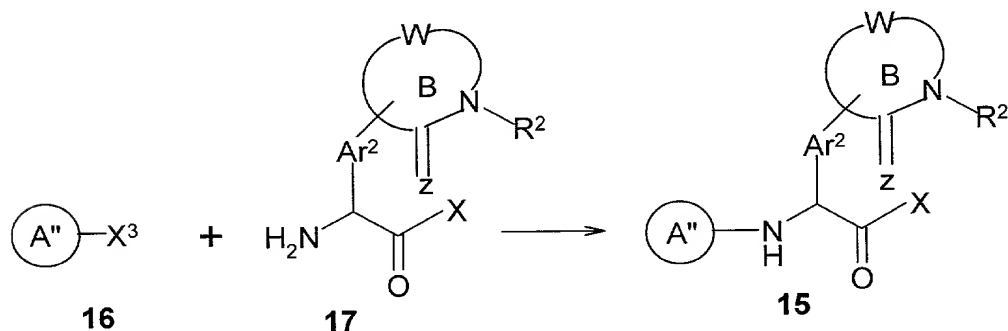
Scheme 4



where  $A''$  is heteroaryl or substituted heteroaryl containing two nitrogen atoms in the heteroaryl ring, and  $B$ ,  $Ar^1$ ,  $Ar^2$ , and  $X$  (preferably alkoxy) are as defined herein. Typically, this reaction is conducted using rhodium acetate dimer,  $Rh_2(OAc)_4$ , in an inert diluent such as toluene at a temperature ranging from about  $25^\circ C$  to about  $80^\circ C$  for about 1 to 12 hours to afford **15**. This reaction is described further in B. R. Henke et. al., *J. Med. Chem.* **1998**, *41*, 5020-5036 and references cited therein.

Similarly, certain compounds of this invention can be prepared by the copper-catalyzed coupling reaction shown in Scheme 5:

Scheme 5



where  $A''$  is as defined herein,  $X^3$  is halogen, such as chloro, bromo or iodo (preferably iodo) and  $B$ ,  $Ar^1$ ,  $Ar^2$ , and  $X$  (preferably alkoxy) are as defined

5        herein. Typically, this reaction is conducted using copper iodide (CuI) and  
potassium carbonate in an inert diluent such as *N,N*-dimethyl acetamide  
(DMA) at a temperature ranging from about 60°C to about 120°C for about  
12 to 36 hours to afford **15**. This reaction is described further in D. Ma et.  
al., *J. Am. Chem. Soc.* **1998**, *120*, 12459-12467 and references cited therein.  
10        It should be recognized by one skilled in the art that although Applicants  
have depicted use of amino acid of formula (a) in the above schemes that one  
could readily use amino acid of formula (b) in the above reactions to get to  
compound of Formula (Ib).

15                For ease of synthesis, the compounds of this invention are typically  
prepared as an ester, i.e., where X is an alkoxy or substituted alkoxy group  
and the like. If desired, the ester group can be hydrolysed using conventional  
conditions and reagents to provide the corresponding carboxylic acid.  
Typically, this reaction is conducted by treating the ester with at least one  
20        equivalent of an alkali metal hydroxide, such as lithium, sodium or potassium  
hydroxide, in an inert diluent, such as methanol or mixtures of methanol and  
water, at a temperature ranging about 0°C to about 24°C for about 1 to about  
12 hours. Alternatively, benzyl esters may be removed by hydrogenolysis  
using a palladium catalyst, such as palladium on carbon, and *tert*-butyl esters  
25        can be removed using formic acid to afford the corresponding carboxylic  
acid.

30                As will be apparent to those skilled in the art, other functional groups  
present on any of the substituents of the compounds of formulas I-II can be  
readily modified or derivatized either before or after the above-described  
synthetic reactions using well-known synthetic procedures. For example, a  
nitro group present on a substituent of a compound of formula I-II or an  
intermediate thereof may be readily reduced by hydrogenation in the presence  
of a palladium catalyst, such as palladium on carbon, to provide the

5 corresponding amino group. This reaction is typically conducted at a  
temperature of from about 20°C to about 50°C for about 6 to about 24 hours  
in an inert diluent, such as methanol. Compounds having a nitro group on  
the Ar<sup>2</sup> substituent can be prepared, for example, by using a 4-  
nitrophenylalanine derivative and the like in the above-described coupling  
10 reactions.

Similarly, a pyridyl group can be hydrogenated in the presence of a  
platinum catalyst, such as platinum oxide, in an acidic diluent to provide the  
corresponding piperidinyll analogue. Generally, this reaction is conducted by  
15 treating the pyridine compound with hydrogen at a pressure ranging from  
about 20 psi to about 60 psi, preferably about 40 psi, in the presence of the  
catalyst at a temperature of about 20°C to about 50°C for about 2 to about 24  
hours in an acidic diluent, such as a mixture of methanol and aqueous  
hydrochloric acid.

20 Additionally, when the Ar<sup>1</sup> substituent of a compound of formula I-II  
contains a primary or secondary amino group, such amino groups can be  
further derivatized either before or after the above coupling reactions to  
provide, by way of example, amides, sulfonamides, ureas, thioureas,  
25 carbamates, secondary or tertiary amines and the like. Compounds having a  
primary amino group on the Ar<sup>1</sup> substituent may be prepared, for example, by  
reduction of the corresponding nitro compound as described above.

By way of illustration, a compound of formula I-II or an intermediate  
30 thereof having a substituent containing a primary or secondary amino group,  
can be readily *N*-acylated using conventional acylating reagents and  
conditions to provide the corresponding amide. This acylation reaction is  
typically conducted by treating the amino compound with at least one  
equivalent, preferably about 1.1 to about 1.2 equivalents, of a carboxylic acid

5 in the presence of a coupling reagent such as a carbodiimide, BOP reagent  
(benzotriazol-1-yloxy-tris(dimethylamino)phosphonium  
hexafluorophosphonate) and the like, in an inert diluent, such as  
dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N,N*-  
dimethylformamide and the like, at a temperature ranging from about 0°C to  
10 about 37°C for about 4 to about 24 hours. Preferably, a promoter, such as  
*N*-hydroxysuccinimide, 1-hydroxy-benzotriazole and the like, is used to  
facilitate the acylation reaction. Examples of carboxylic acids suitable for use  
in this reaction include, but are not limited to, *N-tert*-  
butyloxycarbonylglycine, *N-tert*-butyloxycarbonyl-L-phenylalanine, *N-tert*-  
15 butyloxycarbonyl-L-aspartic acid benzyl ester, benzoic acid, *N-tert*-  
butyloxycarbonylisonipecotic acid, *N*-methylisonipecotic acid, *N-tert*-  
butyloxycarbonylnipecotic acid, *N-tert*-butyloxycarbonyl-L-  
tetrahydroisoquinoline-3-carboxylic acid, *N*-(toluene-4-sulfonyl)-L-proline  
and the like.

20 Alternatively, a compound of formula I-II or an intermediate thereof  
containing a primary or secondary amino group can be *N*-acylated using an  
acyl halide or a carboxylic acid anhydride to form the corresponding amide.  
This reaction is typically conducted by contacting the amino compound with  
25 at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the  
acyl halide or carboxylic acid anhydride in an inert diluent, such as  
dichloromethane, at a temperature ranging from about -70°C to about 40°C  
for about 1 to about 24 hours. If desired, an acylation catalyst such as 4-  
(*N,N*-dimethylamino)pyridine may be used to promote the acylation reaction.  
30 The acylation reaction is preferably conducted in the presence of a suitable  
base to scavenge the acid generated during the reaction. Suitable bases  
include, by way of example, tertiary amines, such as triethylamine,  
diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the



5 reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like.

10 Examples of acyl halides and carboxylic acid anhydrides suitable for use in this reaction include, but are not limited to, 2-methylpropionyl chloride, trimethylacetyl chloride, phenylacetyl chloride, benzoyl chloride, 2-bromobenzoyl chloride, 2-methylbenzoyl chloride, 2-trifluoro-methylbenzoyl chloride, isonicotinoyl chloride, nicotinoyl chloride, picolinoyl chloride, acetic anhydride, succinic anhydride, and the like. Carbamyl chlorides, such as *N,N*-dimethylcarbamyl chloride, *N,N*-diethylcarbamyl chloride and the like, can also be used in this reaction to provide ureas. Similarly, dicarbonates, such as di-*tert*-butyl dicarbonate, may be employed to provide carbamates.

20 In a similar manner, a compound of formula I-II or an intermediate thereof containing a primary or secondary amino group may be *N*-sulfonated to form a sulfonamide using a sulfonyl halide or a sulfonic acid anhydride. Sulfonyl halides and sulfonic acid anhydrides suitable for use in this reaction include, but are not limited to, methanesulfonyl chloride, chloromethanesulfonyl chloride, *p*-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride, and the like. Similarly, sulfamoyl chlorides, such as dimethylsulfamoyl chloride, can be used to provide sulfamides (e.g.,  $>N-SO_2-N<$ ).

30 Additionally, a primary and secondary amino group present on a substituent of a compound of formula I-II or an intermediate thereof can be reacted with an isocyanate or a thioisocyanate to give a urea or thiourea, respectively. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the isocyanate or thioisocyanate in an inert diluent, such as

5       toluene and the like, at a temperature ranging from about 24°C to about 37°C  
for about 12 to about 24 hours. The isocyanates and thioisocyanates used in  
this reaction are commercially available or can be prepared from  
commercially available compounds using well-known synthetic procedures.  
For example, isocyanates and thioisocyanates are readily prepared by reacting  
10       the appropriate amine with phosgene or thiophosgene. Examples of  
isocyanates and thioisocyanates suitable for use in this reaction include, but  
are not limited to, ethyl isocyanate, *n*-propyl isocyanate, 4-cyanophenyl  
isocyanate, 3-methoxyphenyl isocyanate, 2-phenylethyl isocyanate, methyl  
thioisocyanate, ethyl thioisocyanate, 2-phenylethyl thioisocyanate, 3-  
15       phenylpropyl thioisocyanate, 3-(*N,N*-diethylamino)propyl thioisocyanate,  
phenyl thioisocyanate, benzyl thioisocyanate, 3-pyridyl thioisocyanate,  
fluorescein isothiocyanate (isomer I) and the like.

20       Furthermore, when a compound of formula I-II or an intermediate  
thereof contains a primary or secondary amino group, the amino group can be  
reductively alkylated using aldehydes or ketones to form a secondary or  
tertiary amino group. This reaction is typically conducted by contacting the  
amino compound with at least one equivalent, preferably about 1.1 to about  
1.5 equivalents, of an aldehyde or ketone and at least one equivalent based on  
25       the amino compound of a metal hydride reducing agent, such as sodium  
cyanoborohydride, in an inert diluent, such as methanol, tetrahydrofuran,  
mixtures thereof and the like, at a temperature ranging from about 0°C to  
about 50°C for about 1 to about 72 hours. Aldehydes and ketones suitable  
for use in this reaction include, by way of example, benzaldehyde, 4-  
30       chlorobenzaldehyde, valeraldehyde and the like.

In a similar manner, when a compound of formula I-II or an  
intermediate thereof has a substituent containing a hydroxyl group, the  
hydroxyl group can be further modified or derivatized either before or after

5 the above coupling reactions to provide, by way of example, ethers, carbamates and the like.

10 By way of example, a compound of formula I-II or an intermediate thereof having a substituent containing a hydroxyl group, such as where the lactam ring is 4-hydroxypyridone group, can be readily *O*-alkylated to form ethers. This *O*-alkylation reaction is typically conducted by contacting the hydroxy compound with a suitable alkali or alkaline earth metal base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and the like, to form the alkali or alkaline earth metal salt of the hydroxyl group. 15 This salt is generally not isolated, but is reacted *in situ* with at least one equivalent of an alkyl or substituted alkyl halide or sulfonate, such as an alkyl chloride, bromide, iodide, mesylate or tosylate, to afford the ether. Generally, this reaction is conducted at a temperature ranging from about 60°C to about 150°C for about 24 to about 72 hours. Preferably, a catalytic amount of sodium or potassium iodide is added to the reaction mixture when 20 an alkyl chloride or bromide is employed in the reaction.

25 Examples of alkyl or substituted alkyl halides and sulfonates suitable for use in this reaction include, but are not limited to, *tert*-butyl bromoacetate, *N*-*tert*-butyl chloroacetamide, 1-bromoethylbenzene, ethyl  $\alpha$ -bromophenylacetate, 2-(*N*-ethyl-*N*-phenylamino)ethyl chloride, 2-(*N,N*-ethylamino)ethyl chloride, 2-(*N,N*-diisopropylamino)ethyl chloride, 2-(*N,N*-dibenzylamino)ethyl chloride, 3-(*N,N*-ethylamino)propyl chloride, 3-(*N*-benzyl-*N*-methylamino)propyl chloride, *N*-(2-chloroethyl)morpholine, 2- 30 (hexamethyleneimino)ethyl chloride, 3-(*N*-methylpiperazine)propyl chloride, 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine, 2-(4-hydroxy-4-phenylpiperidine)ethyl chloride, *N*-*tert*-butyloxycarbonyl-3-piperidinemethyl tosylate, and the like.

5                   Alternatively, a hydroxyl group present on a substituent of a  
compound of formula I-II or an intermediate thereof can be *O*-alkylating using  
the Mitsunobu reaction. In this reaction, an alcohol, such as 3-(*N,N*-  
dimethylamino)-1-propanol and the like, is reacted with about 1.0 to about  
1.3 equivalents of triphenylphosphine and about 1.0 to about 1.3 equivalents  
10                   of diethyl azodicarboxylate in an inert diluent, such as tetrahydrofuran, at a  
temperature ranging from about -10°C to about 5°C for about 0.25 to about 1  
hour. About 1.0 to about 1.3 equivalents of a hydroxy compound, such as *N*-  
*tert*-butyltyrosine methyl ester, is then added and the reaction mixture is  
stirred at a temperature of about 0°C to about 30°C for about 2 to about 48  
15                   hours to provide the *O*-alkylated product.

                  In a similar manner, a compound of formula I-II or an intermediate  
thereof containing an aryl hydroxy group can be reacted with an aryl iodide to  
provide a diaryl ether. Generally, this reaction is conducted by forming the  
alkali metal salt of the hydroxyl group using a suitable base, such as sodium  
20                   hydride, in an inert diluent such as xylenes at a temperature of about -25°C to  
about 10°C. The salt is then treated with about 1.1 to about 1.5 equivalents  
of cuprous bromide dimethyl sulfide complex at a temperature ranging from  
about 10°C to about 30°C for about 0.5 to about 2.0 hours, followed by  
25                   about 1.1 to about 1.5 equivalents of an aryl iodide, such as sodium 2-  
iodobenzoate and the like. The reaction is then heated to about 70°C to about  
150°C for about 2 to about 24 hours to provide the diaryl ether.

                  Additionally, a hydroxy-containing compound can also be readily  
30                   derivatized to form a carbamate. In one method for preparing such  
carbamates, a hydroxy compound of formula I-II or an intermediate thereof is  
contacted with about 1.0 to about 1.2 equivalents of 4-nitrophenyl  
chloroformate in an inert diluent, such as dichloromethane, at a temperature  
ranging from about -25°C to about 0°C for about 0.5 to about 2.0 hours.

5 Treatment of the resulting carbonate with an excess, preferably about 2 to  
about 5 equivalents, of a trialkylamine, such as triethylamine, for about 0.5 to  
2 hours, followed by about 1.0 to about 1.5 equivalents of a primary or  
secondary amine provides the carbamate. Examples of amines suitable for  
using in this reaction include, but are not limited to, piperazine, 1-  
10 methylpiperazine, 1-acetylpiperazine, morpholine, thiomorpholine,  
pyrrolidine, piperidine and the like.

15 Alternatively, in another method for preparing carbamates, a hydroxy-  
containing compound is contacted with about 1.0 to about 1.5 equivalents of a  
carbamyl chloride in an inert diluent, such as dichloromethane, at a  
temperature ranging from about 25°C to about 70°C for about 2 to about 72  
hours. Typically, this reaction is conducted in the presence of a suitable base  
to scavenge the acid generated during the reaction. Suitable bases include, by  
way of example, tertiary amines, such as triethylamine,  
20 diisopropylethylamine, *N*-methylmorpholine and the like. Additionally, at  
least one equivalent (based on the hydroxy compound) of 4-(*N,N*-  
dimethylamino)pyridine is preferably added to the reaction mixture to  
facilitate the reaction. Examples of carbamyl chlorides suitable for use in this  
reaction include, by way of example, dimethylcarbamyl chloride,  
25 diethylcarbamyl chloride and the like.

30 Likewise, when a compound of formula I-II or an intermediate thereof  
contains a primary or secondary hydroxyl group, such hydroxyl groups can  
be readily converted into a leaving group and displaced to form, for example,  
amines, sulfides and fluorides. Generally, when a chiral compound is  
employed in these reactions, the stereochemistry at the carbon atom attached  
to the derivatized hydroxyl group is typically inverted.

5           These reactions are typically conducted by first converting the  
hydroxyl group into a leaving group, such as a tosylate, by treatment of the  
hydroxy compound with at least one equivalent of a sulfonyl halide, such as  
*p*-toluenesulfonyl chloride and the like, in pyridine. This reaction is  
generally conducted at a temperature of from about 0°C to about 70°C for  
10       about 1 to about 48 hours. The resulting tosylate can then be readily  
displaced with sodium azide, for example, by contacting the tosylate with at  
least one equivalent of sodium azide in an inert diluent, such as a mixture of  
*N,N*-dimethylformamide and water, at a temperature ranging from about 0°C  
15       to about 37°C for about 1 to about 12 hours to provide the corresponding  
azido compound. The azido group can then be reduced by, for example,  
hydrogenation using a palladium on carbon catalyst to provide the amino  
(-NH<sub>2</sub>) compound.

20           Similarly, a tosylate group can be readily displaced by a thiol to form  
a sulfide. This reaction is typically conducted by contacting the tosylate with  
at least one equivalent of a thiol, such as thiophenol, in the presence of a  
suitable base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in an inert  
diluent, such as *N,N*-dimethylformamide, at a temperature of from about 0°C  
to about 37°C for about 1 to about 12 hours to provide the sulfide.

25       Additionally, treatment of a tosylate with morpholinosulfur trifluoride in an  
inert diluent, such as dichloromethane, at a temperature ranging from about  
0°C to about 37°C for about 12 to about 24 hours affords the corresponding  
fluoro compound.

30           Furthermore, a compound of formula I-II or an intermediate thereof  
having a substituent containing an iodoaryl group can be readily converted  
either before or after the above coupling reactions into a biaryl compound.  
Typically, this reaction is conducted by treating the iodoaryl compound with  
about 1.1 to about 2 equivalents of an arylzinc iodide, such as 2-

5 (methoxycarbonyl)phenylzinc iodide, in the presence of a palladium catalyst,  
such as palladium tetra(triphenylphosphine), in an inert diluent, such as  
tetrahydrofuran, at a temperature ranging from about 24°C to about 30°C  
until reaction completion. This reaction is further described, for example, in  
Rieke, *J. Org. Chem.* **1991**, 56, 1445. Additional methods for preparing  
10 biaryl derivatives are disclosed in International Publication Number WO  
98/53817, published December 3, 1998, the disclosure of which is  
incorporated herein by reference in its entirety.

15 In some cases, the compounds of formula I-II or intermediates thereof  
may contain substituents having one or more sulfur atoms. When present,  
such sulfur atoms can be oxidized either before or after the above coupling  
reactions to provide a sulfoxide or sulfone compound using conventional  
reagents and reaction conditions. Suitable reagents for oxidizing a sulfide  
compound to a sulfoxide include, by way of example, hydrogen peroxide, 3-  
20 chloroperoxybenzoic acid (MCPBA), sodium periodate and the like. The  
oxidation reaction is typically conducted by contacting the sulfide compound  
with about 0.95 to about 1.1 equivalents of the oxidizing reagent in an inert  
diluent, such as dichloromethane, at a temperature ranging from about -50°C  
to about 75°C for about 1 to about 24 hours. The resulting sulfoxide can then  
25 be further oxidized to the corresponding sulfone by contacting the sulfoxide  
with at least one additional equivalent of an oxidizing reagent, such as  
hydrogen peroxide, MCPBA, potassium permanganate and the like.  
Alternatively, the sulfone can be prepared directly by contacting the sulfide  
with at least two equivalents, and preferably an excess, of the oxidizing  
30 reagent. Such reactions are described further in March, "*Advanced Organic  
Chemistry*", 4th Ed., pp. 1201-1202, Wiley Publisher, 1992.

Other procedures and reaction conditions for preparing the compounds  
of this invention are described in the examples set forth below. Additionally,

5 other procedures for preparing compounds useful in certain aspects of this  
invention are disclosed in U.S. Applications Serial Nos. 09/489,377 and  
09/489,378, filed on January 21, 2000, entitled "Compounds Which Inhibit  
Leucocyte Adhesion Mediated by VLA-4" (Attorney Docket Nos. 002010-  
517 and 002010-525); the disclosure of which is incorporated herein by  
10 reference in its entirety.

#### Pharmaceutical Formulations

15 When employed as pharmaceuticals, the compounds of this invention  
are usually administered in the form of pharmaceutical compositions. These  
compounds can be administered by a variety of routes including oral, rectal,  
transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These  
compounds are effective as both injectable and oral compositions. Such  
compositions are prepared in a manner well known in the pharmaceutical art  
and comprise at least one active compound.

20 This invention also includes pharmaceutical compositions which  
contain, as the active ingredient, one or more of the compounds of formula I-  
VII above associated with pharmaceutically acceptable carriers. In making  
the compositions of this invention, the active ingredient is usually mixed with  
25 an excipient, diluted by an excipient or enclosed within such a carrier which  
can be in the form of a capsule, sachet, paper or other container. The  
excipient employed is typically an excipient suitable for administration to  
human subjects or other mammals. When the excipient serves as a diluent, it  
can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier  
30 or medium for the active ingredient. Thus, the compositions can be in the  
form of tablets, pills, powders, lozenges, sachets, cachets, elixirs,  
suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid  
medium), ointments containing, for example, up to 10% by weight of the



5 active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

10 In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

15 Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

25 The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

5           The active compound is effective over a wide dosage range and is  
generally administered in a pharmaceutically effective amount. It, will be  
understood, however, that the amount of the compound actually administered  
will be determined by a physician, in the light of the relevant circumstances,  
including the condition to be treated, the chosen route of administration, the  
10       actual compound administered, the age, weight, and response of the  
individual patient, the severity of the patient's symptoms, and the like.

15           For preparing solid compositions such as tablets, the principal active  
ingredient is mixed with a pharmaceutical excipient to form a solid  
preformulation composition containing a homogeneous mixture of a  
compound of the present invention. When referring to these preformulation  
compositions as homogeneous, it is meant that the active ingredient is  
dispersed evenly throughout the composition so that the composition may be  
readily subdivided into equally effective unit dosage forms such as tablets,  
20       pills and capsules. This solid preformulation is then subdivided into unit  
dosage forms of the type described above containing from, for example, 0.1  
to about 500 mg of the active ingredient of the present invention.

25           The tablets or pills of the present invention may be coated or  
otherwise compounded to provide a dosage form affording the advantage of  
prolonged action. For example, the tablet or pill can comprise an inner  
dosage and an outer dosage component, the latter being in the form of an  
envelope over the former. The two components can be separated by an  
enteric layer which serves to resist disintegration in the stomach and permit  
30       the inner component to pass intact into the duodenum or to be delayed in  
release. A variety of materials can be used for such enteric layers or  
coatings, such materials including a number of polymeric acids and mixtures  
of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose  
acetate.

5           The liquid forms in which the novel compositions of the present  
invention may be incorporated for administration orally or by injection  
include aqueous solutions suitably flavored syrups, aqueous or oil  
suspensions, and flavored emulsions with edible oils such as cottonseed oil,  
sesame oil, coconut oil, or peanut oil, as well as elixirs and similar  
10           pharmaceutical vehicles.

15           Compositions for inhalation or insufflation include solutions and  
suspensions in pharmaceutically acceptable, aqueous or organic solvents, or  
mixtures thereof, and powders. The liquid or solid compositions may contain  
suitable pharmaceutically acceptable excipients as described *supra*.  
Preferably the compositions are administered by the oral or nasal respiratory  
route for local or systemic effect. Compositions in preferably  
pharmaceutically acceptable solvents may be nebulized by use of inert gases.  
Nebulized solutions may be breathed directly from the nebulizing device or  
20           the nebulizing device may be attached to a face masks tent, or intermittent  
positive pressure breathing machine. Solution, suspension, or powder  
compositions may be administered, preferably orally or nasally, from devices  
which deliver the formulation in an appropriate manner.

25           The following formulation examples illustrate the pharmaceutical  
compositions of the present invention.

Formulation Example 1

30           Hard gelatin capsules containing the following ingredients are  
prepared:

<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

5           The above ingredients are mixed and filled into hard gelatin capsules  
in 340 mg quantities.

#### Formulation Example 2

A tablet formula is prepared using the ingredients below:

10	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
	Active Ingredient	25.0
	Cellulose, microcrystalline	200.0
15	Colloidal silicon dioxide	10.0
	Stearic acid	5.0

The components are blended and compressed to form tablets, each  
weighing 240 mg.

#### Formulation Example 3

A dry powder inhaler formulation is prepared containing the following  
components:

25	<u>Ingredient</u>	<u>Weight %</u>
	Active Ingredient	5
	Lactose	95

30           The active mixture is mixed with the lactose and the mixture is added  
to a dry powder inhaling appliance.

#### Formulation Example 4

35           Tablets, each containing 30 mg of active ingredient, are prepared as  
follows:

5		Quantity
	<u>Ingredient</u>	<u>(mg/tablet)</u>
	Active Ingredient	30.0 mg
	Starch	45.0 mg
10	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone	
	(as 10% solution in water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
15	Talc	<u>1.0 mg</u>
	Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

#### Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

30		Quantity
	<u>Ingredient</u>	<u>(mg/capsule)</u>
	Active Ingredient	40.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
35	Total	150.0 mg

The active ingredient, cellulose, starch, an magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

<u>Ingredient</u>	<u>Amount</u>
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

<u>Ingredient</u>	<u>Amount</u>
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%)	
Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 ml

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water.

The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

<u>Ingredient</u>	<u>Quantity (mg/capsule)</u>
Active Ingredient	15.0 mg
Starch	407.0 mg
Magnesium stearate	<u>3.0 mg</u>
Total	425.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

Formulation Example 9

An intravenous formulation may be prepared as follows:

<u>Ingredient</u>	<u>Quantity</u>
Active Ingredient	250.0 mg
Isotonic saline	1000 ml

Formulation Example 10

A topical formulation may be prepared as follows:

<u>Ingredient</u>	<u>Quantity</u>
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

5 Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of  
10 pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

15 Direct or indirect placement techniques may be used when it is desirable or necessary to introduce the pharmaceutical composition to the brain. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to  
20 specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

25 Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by  
30 intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.



## Utility

The compounds of this invention can be employed to bind VLA-4 ( $\alpha_4\beta_1$  integrin) in biological samples, i.e., the compounds bind VLA-4 with an  $IC_{50}$  of 15  $\mu$ M or less in a competitive binding assay as described herein. Accordingly, these compounds have utility in, for example, assaying such samples for VLA-4. In such assays, the compounds can be bound to a solid support and the VLA-4 sample added thereto. The amount of VLA-4 in the sample can be determined by conventional methods such as use of a sandwich ELISA assay. Alternatively, labeled VLA-4 can be used in a competitive assay to measure for the presence of VLA-4 in the sample. Other suitable assays are well known in the art.

In addition, certain of the compounds of this invention inhibit, *in vivo*, adhesion of leukocytes to endothelial cells mediated by VLA-4 by competitive binding to VLA-4. Accordingly, the compounds of this invention can be used in the treatment of diseases mediated by VLA-4 or leucocyte adhesion. Such diseases include inflammatory diseases in mammalian patients such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

The biological activity of the compounds identified above may be assayed in a variety of systems. For example, a compound can be immobilized on a solid surface and adhesion of cells expressing VLA-4 can be measured. Using such formats, large numbers of compounds can be screened. Cells suitable for this assay include any leukocytes known to express VLA-4 such

5 as T cells, B cells, monocytes, eosinophils, and basophils. A number of leukocyte cell lines can also be used, examples include Jurkat and U937.

10 The test compounds can also be tested for the ability to competitively inhibit binding between VLA-4 and VCAM-1, or between VLA-4 and a labeled compound known to bind VLA-4 such as a compound of this invention or antibodies to VLA-4. In these assays, the VCAM-1 can be immobilized on a solid surface. VCAM-1 may also be expressed as a recombinant fusion protein having an Ig tail (e.g., IgG) so that binding to VLA-4 may be detected in an immunoassay. Alternatively, VCAM-1  
15 expressing cells, such as activated endothelial cells or VCAM-1 transfected fibroblasts can be used. For assays to measure the ability to block adhesion to brain endothelial cells, the assays described in International Patent Application Publication No. WO 91/05038 are particularly preferred. This application is incorporated herein by reference in its entirety.

20 Many assay formats employ labelled assay components. The labelling systems can be in a variety of forms. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide variety of labels may be used. The component may  
25 be labelled by any one of several methods. The most common method of detection is the use of autoradiography with  $^3\text{H}$ ,  $^{125}\text{I}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$ , or  $^{32}\text{P}$  labelled compounds or the like. Non-radioactive labels include ligands which bind to labelled antibodies, fluorophores, chemiluminescent agents, enzymes and antibodies which can serve as specific binding pair members for a labelled  
30 ligand. The choice of label depends on sensitivity required, ease of conjugation with the compound, stability requirements, and available instrumentation.

5           Appropriate *in vivo* models for demonstrating efficacy in treating inflammatory responses include EAE (experimental autoimmune encephalomyelitis) in mice, rats, guinea pigs or primates, as well as other inflammatory models dependent upon  $\alpha 4$  integrins.

10           Compounds having the desired biological activity may be modified as necessary to provide desired properties such as improved pharmacological properties (e.g., *in vivo* stability, bio-availability), or the ability to be detected in diagnostic applications. Stability can be assayed in a variety of ways such as by measuring the half-life of the proteins during incubation with peptidases or human plasma or serum. A number of such protein stability assays have been described (see, e.g., Verhoef et al., Eur. J. Drug Metab. Pharmacokinet., 1990, 15(2):83-93).

20           For diagnostic purposes, a wide variety of labels may be linked to the compounds, which may provide, directly or indirectly, a detectable signal. Thus, the compounds of the subject invention may be modified in a variety of ways for a variety of end purposes while still retaining biological activity. In addition, various reactive sites may be introduced at the terminus for linking to particles, solid substrates, macromolecules, or the like.

25           Labeled compounds can be used in a variety of *in vivo* or *in vitro* applications. A wide variety of labels may be employed, such as radionuclides (e.g., gamma-emitting radioisotopes such as technetium-99 or indium-111), fluorescers (e.g., fluorescein), enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, chemiluminescent compounds, bioluminescent compounds, and the like. Those of ordinary skill in the art will know of other suitable labels for binding to the complexes, or will be able to ascertain such using routine experimentation. The binding of these

30

5 labels is achieved using standard techniques common to those of ordinary skill in the art.

10 *In vitro* uses include diagnostic applications such as monitoring inflammatory responses by detecting the presence of leukocytes expressing VLA-4. The compounds of this invention can also be used for isolating or labeling such cells. In addition, as mentioned above, the compounds of the invention can be used to assay for potential inhibitors of VLA-4/VCAM-1 interactions.

15 For *in vivo* diagnostic imaging to identify, e.g., sites of inflammation, radioisotopes are typically used in accordance with well known techniques. The radioisotopes may be bound to the peptide either directly or indirectly using intermediate functional groups. For instance, chelating agents such as diethylenetriaminepentaacetic acid (DTPA) and ethylenediaminetetraacetic acid (EDTA) and similar molecules have been used to bind proteins to metallic ion  
20 radioisotopes.

25 The complexes can also be labeled with a paramagnetic isotope for purposes of *in vivo* diagnosis, as in magnetic resonance imaging (MRI) or electron spin resonance (ESR), both of which are well known. In general, any conventional method for visualizing diagnostic imaging can be used. Usually gamma- and positron-emitting radioisotopes are used for camera imaging and paramagnetic isotopes are used for MRI. Thus, the compounds can be used to monitor the course of amelioration of an inflammatory  
30 response in an individual. By measuring the increase or decrease in lymphocytes expressing VLA-4 it is possible to determine whether a particular therapeutic regimen aimed at ameliorating the disease is effective.

5           The pharmaceutical compositions of the present invention can be used to  
block or inhibit cellular adhesion associated with a number of diseases and  
disorders. For instance, a number of inflammatory disorders are associated  
with integrins or leukocytes. Treatable disorders include, e.g.,  
transplantation rejection (e.g., allograft rejection), Alzheimer's disease,  
10   atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset  
diabetes), retinitis, cancer metastases, rheumatoid arthritis, acute  
leukocyte-mediated lung injury (e.g., adult respiratory distress syndrome),  
asthma, nephritis, and acute and chronic inflammation, including atopic  
dermatitis, psoriasis, myocardial ischemia, and inflammatory bowel disease  
15   (including Crohn's disease and ulcerative colitis). In preferred embodiments  
the pharmaceutical compositions are used to treat inflammatory brain  
disorders, such as multiple sclerosis (MS), viral meningitis and encephalitis.

          Inflammatory bowel disease is a collective term for two similar diseases  
referred to as Crohn's disease and ulcerative colitis. Crohn's disease is an  
idiopathic, chronic ulceroconstrictive inflammatory disease characterized by  
sharply delimited and typically transmural involvement of all layers of the  
bowel wall by a granulomatous inflammatory reaction. Any segment of the  
gastrointestinal tract, from the mouth to the anus, may be involved, although  
20   the disease most commonly affects the terminal ileum and/or colon.  
Ulcerative colitis is an inflammatory response limited largely to the colonic  
mucosa and submucosa. Lymphocytes and macrophages are numerous in  
lesions of inflammatory bowel disease and may contribute to inflammatory  
injury.

          Asthma is a disease characterized by increased responsiveness of the  
tracheobronchial tree to various stimuli potentiating paroxysmal constriction  
of the bronchial airways. The stimuli cause release of various mediators of  
inflammation from IgE-coated mast cells including histamine, eosinophilic

5 and neutrophilic chemotactic factors, leukotrienes, prostaglandin and platelet activating factor. Release of these factors recruits basophils, eosinophils and neutrophils, which cause inflammatory injury.

10 Atherosclerosis is a disease of arteries (e.g., coronary, carotid, aorta and iliac). The basic lesion, the atheroma, consists of a raised focal plaque within the intima, having a core of lipid and a covering fibrous cap. Atheromas compromise arterial blood flow and weaken affected arteries. Myocardial and cerebral infarcts are a major consequence of this disease. Macrophages and leukocytes are recruited to atheromas and contribute to inflammatory injury.

15 Rheumatoid arthritis is a chronic, relapsing inflammatory disease that primarily causes impairment and destruction of joints. Rheumatoid arthritis usually first affects the small joints of the hands and feet but then may involve the wrists, elbows, ankles and knees. The arthritis results from interaction of synovial cells with leukocytes that infiltrate from the circulation into the synovial lining of the joints. See e.g., Paul, *Immunology* (3d ed., Raven Press, 1993).

25 Another indication for the compounds of this invention is in treatment of organ or graft rejection mediated by VLA-4. Over recent years there has been a considerable improvement in the efficiency of surgical techniques for transplanting tissues and organs such as skin, kidney, liver, heart, lung, pancreas and bone marrow. Perhaps the principal outstanding problem is the lack of satisfactory agents for inducing immunotolerance in the recipient to the transplanted allograft or organ. When allogeneic cells or organs are transplanted into a host (i.e., the donor and donee are different individuals from the same species), the host immune system is likely to mount an immune response to foreign antigens in the transplant (host-versus-graft disease)

30

5 leading to destruction of the transplanted tissue. CD8<sup>+</sup> cells, CD4 cells and monocytes are all involved in the rejection of transplant tissues. Compounds of this invention which bind to alpha-4 integrin are useful, *inter alia*, to block alloantigen-induced immune responses in the donee thereby preventing such cells from participating in the destruction of the transplanted tissue or organ. See, *e.g.*, Paul et al., *Transplant International* 9, 420-425 (1996); 10 Georczynski et al., *Immunology* 87, 573-580 (1996); Georczynski et al., *Transplant. Immunol.* 3, 55-61 (1995); Yang et al., *Transplantation* 60, 71-76 (1995); Anderson et al., *APMIS* 102, 23-27 (1994).

15 A related use for compounds of this invention which bind to VLA-4 is in modulating the immune response involved in "graft versus host" disease (GVHD). See *e.g.*, Schlegel et al., *J. Immunol.* 155, 3856-3865 (1995). GVHD is a potentially fatal disease that occurs when immunologically competent cells are transferred to an allogeneic recipient. In this situation, 20 the donor's immunocompetent cells may attack tissues in the recipient. Tissues of the skin, gut epithelia and liver are frequent targets and may be destroyed during the course of GVHD. The disease presents an especially severe problem when immune tissue is being transplanted, such as in bone marrow transplantation; but less severe GVHD has also been reported in 25 other cases as well, including heart and liver transplants. The therapeutic agents of the present invention are used, *inter alia*, to block activation of the donor T-cells thereby interfering with their ability to lyse target cells in the host.

30 A further use of the compounds of this invention is inhibiting tumor metastasis. Several tumor cells have been reported to express VLA-4 and compounds which bind VLA-4 block adhesion of such cells to endothelial cells. Steinback et al., *Urol. Res.* 23, 175-83 (1995); Orosz et al., *Int. J.*

5        *Cancer* 60, 867-71 (1995); Freedman et al., *Leuk. Lymphoma* 13, 47-52  
(1994); Okahara et al., *Cancer Res.* 54, 3233-6 (1994).

10        A further use of the compounds of this invention is in treating multiple  
sclerosis. Multiple sclerosis is a progressive neurological autoimmune  
disease that affects an estimated 250,000 to 350,000 people in the United  
States. Multiple sclerosis is thought to be the result of a specific autoimmune  
reaction in which certain leukocytes attack and initiate the destruction of  
myelin, the insulating sheath covering nerve fibers. In an animal model for  
multiple sclerosis, murine monoclonal antibodies directed against VLA-4  
15        have been shown to block the adhesion of leukocytes to the endothelium, and  
thus prevent inflammation of the central nervous system and subsequent  
paralysis in the animals<sup>16</sup>.

20        Pharmaceutical compositions of the invention are suitable for use in a  
variety of drug delivery systems. Suitable formulations for use in the present  
invention are found in *Remington's Pharmaceutical Sciences*, Mace  
Publishing Company, Philadelphia, PA, 17th ed. (1985).

25        In order to enhance serum half-life, the compounds may be encapsulated,  
introduced into the lumen of liposomes, prepared as a colloid, or other  
conventional techniques may be employed which provide an extended serum  
half-life of the compounds. A variety of methods are available for preparing  
liposomes, as described in, e.g., Szoka, et al., U.S. Patent Nos. 4,235,871,  
4,501,728 and 4,837,028 each of which is incorporated herein by reference.

30        The amount administered to the patient will vary depending upon what is  
being administered, the purpose of the administration, such as prophylaxis or  
therapy, the state of the patient, the manner of administration, and the like.  
In therapeutic applications, compositions are administered to a patient already



5 suffering from a disease in an amount sufficient to cure or at least partially  
arrest the symptoms of the disease and its complications. An amount  
adequate to accomplish this is defined as "therapeutically effective dose."  
Amounts effective for this use will depend on the disease condition being  
treated as well as by the judgment of the attending clinician depending upon  
10 factors such as the severity of the inflammation, the age, weight and general  
condition of the patient, and the like.

The compositions administered to a patient are in the form of  
pharmaceutical compositions described above. These compositions may be  
sterilized by conventional sterilization techniques, or may be sterile filtered.  
The resulting aqueous solutions may be packaged for use as is, or lyophilized,  
the lyophilized preparation being combined with a sterile aqueous carrier  
prior to administration. The pH of the compound preparations typically will  
be between 3 and 11, more preferably from 5 to 9 and most preferably from 7  
20 to 8. It will be understood that use of certain of the foregoing excipients,  
carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention will  
vary according to, for example, the particular use for which the treatment is  
made, the manner of administration of the compound, the health and  
25 condition of the patient, and the judgment of the prescribing physician. For  
example, for intravenous administration, the dose will typically be in the  
range of about 20  $\mu\text{g}$  to about 500  $\mu\text{g}$  per kilogram body weight, preferably  
about 100  $\mu\text{g}$  to about 300  $\mu\text{g}$  per kilogram body weight. Suitable dosage  
ranges for intranasal administration are generally about 0.1  $\mu\text{g}$  to 1 mg per  
30 kilogram body weight. Effective doses can be extrapolated from  
dose-response curves derived from *in vitro* or animal model test systems.

5           Compounds of this invention are also capable of binding or antagonizing  
the actions of  $\alpha_6\beta_1$ ,  $\alpha_9\beta_1$ ,  $\alpha_4\beta_7$ ,  $\alpha_d\beta_2$ ,  $\alpha_e\beta_7$  integrins (although  $\alpha_4\beta_1$  and  $\alpha_9\beta_1$   
are preferred in this invention). Accordingly, compounds of this invention  
are also useful for preventing or reversing the symptoms, disorders or  
diseases induced by the binding of these integrins to their respective ligands.

10           For example, International Publication Number WO 98/53817, published  
December 3, 1998 (the disclosure of which is incorporated herein by  
reference in its entirety) and references cited therein describe disorders  
mediated by  $\alpha_4\beta_7$ . This reference also describes an assay for determining  
antagonism of  $\alpha_4\beta_7$  dependent binding to VCAM-Ig fusion protein.

15           Additionally, compounds that bind  $\alpha_d\beta_2$  and  $\alpha_e\beta_7$  integrins are  
particularly useful for the treatment of asthma and related lung diseases. See,  
for example, M. H. Grayson et al., *J. Exp. Med.* **1998**, 188(11) 2187-2191.  
20           Compounds that bind  $\alpha_e\beta_7$  integrin are also useful for the treatment of  
systemic lupus erythematosus (see, for example, M. Pang et al., *Arthritis*  
*Rheum.* **1998**, 41(8), 1456-1463); Crohn's disease, ulcerative colitis and  
inflammatory bowel disease (IBD) (see, for example, D. Elewaut et al., *Scand*  
*J. Gastroenterol* **1998**, 33(7) 743-748); Sjogren's syndrome (see, for  
25           example, U. Kroneld et al., *Scand J. Gastroenterol* **1998**, 27(3), 215-218);  
and rheumatoid arthritis (see, for example, *Scand J. Gastroenterol* **1996**,  
44(3), 293-298). And compounds that bind  $\alpha_6\beta_1$  may be useful in preventing  
fertilization (see, for example, H. Chen et al., *Chem. Biol.* **1999**, 6, 1-10).

30           Certain of the compounds within the generic formulas described herein  
are also useful as synthetic intermediates for other compounds of this  
invention as illustrated in the examples herein.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

## EXAMPLES

In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

15	aq or aq.	=	aqueous
	AcOH	=	acetic acid
	bd	=	broad doublet
	bm	=	broad multiplet
	bs	=	broad singlet
	Bn	=	benzyl
20	Boc	=	<i>N</i> - <i>tert</i> -butoxycarbonyl
	Boc <sub>2</sub> O	=	di- <i>tert</i> -butyl dicarbonate
	BOP	=	benzotriazol-1-yloxy- tris(dimethylamino)phosphonium hexafluorophosphate
25	Cbz	=	carbobenzyloxy
	CHCl <sub>3</sub>	=	chloroform
	CH <sub>2</sub> Cl <sub>2</sub>	=	dichloromethane
	(COCl) <sub>2</sub>	=	oxalyl chloride
	d	=	doublet
30	dd	=	doublet of doublets
	dt	=	doublet of triplets
	DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCC	=	1,3-dicyclohexylcarbodiimide
	DMAP	=	4- <i>N,N</i> -dimethylaminopyridine
35	DME	=	ethylene glycol dimethyl ether
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethylsulfoxide
	EDC	=	1-(3-dimethylaminopropyl)-3- ethylcarbodiimide hydrochloride
40	Et <sub>3</sub> N	=	triethylamine
	Et <sub>2</sub> O	=	diethyl ether
	EtOAc	=	ethyl acetate
	EtOH	=	ethanol
	eq or eq.	=	equivalent
45	Fmoc	=	<i>N</i> -(9-fluorenylmethoxycarbonyl)

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5	FmocONSu	=	<i>N</i> -(9-fluorenylmethoxycarbonyl)-succinimide
	g	=	grams
	h	=	hour
	H <sub>2</sub> O	=	water
10	HBr	=	hydrobromic acid
	HCl	=	hydrochloric acid
	HOBT	=	1-hydroxybenzotriazole hydrate
	hr	=	hour
	K <sub>2</sub> CO <sub>3</sub>	=	potassium carbonate
15	L	=	liter
	m	=	multiplet
	MeOH	=	methanol
	mg	=	milligram
	MgSO <sub>4</sub>	=	magnesium sulfate
20	mL	=	milliliter
	mm	=	millimeter
	mM	=	millimolar
	mmol	=	millimol
	mp	=	melting point
25	N	=	normal
	NaCl	=	sodium chloride
	Na <sub>2</sub> CO <sub>3</sub>	=	sodium carbonate
	NaHCO <sub>3</sub>	=	sodium bicarbonate
	NaOEt	=	sodium ethoxide
30	NaOH	=	sodium hydroxide
	NH <sub>4</sub> Cl	=	ammonium chloride
	NMM	=	<i>N</i> -methylmorpholine
	Phe	=	L-phenylalanine
	Pro	=	L-proline
35	psi	=	pounds per square inch
	PtO <sub>2</sub>	=	platinum oxide
	q	=	quartet
	quint.	=	quintet
	rt	=	room temperature
40	s	=	singlet
	sat	=	saturated
	t	=	triplet
	<i>t</i> -BuOH	=	<i>tert</i> -butanol
	TFA	=	trifluoroacetic acid
45	THF	=	tetrahydrofuran
	TLC or tlc	=	thin layer chromatography
	Ts	=	tosyl
	TsCl	=	tosyl chloride
	TsOH	=	tosylate

5                     $\mu\text{L}$                     =                    microliter

The following Methods may be used to prepare the compounds of this invention.

10                    Method A

2,4-Dihydroxy-3-iodopyridine Preparation Procedure

15                    A mixture of 2,4-dihydroxypyridine (1.0 eq),  $\text{K}_2\text{CO}_3$  (1.0 eq), and water was stirred at 100 °C so that it became homogeneous. With continued stirring and heating,  $\text{I}_2$  (1.0 eq) was added in portions, causing the evolution of gas. When the solid  $\text{I}_2$  was consumed, the mixture was cooled and acidified with aqueous  $\text{KHSO}_4$  (1.0 eq), generating a precipitate. The precipitate was collected by filtration, rinsed with water, and stored under high vacuum, to give 2,4-dihydroxy-3-iodopyridine.

20                    Method B

1-Methyl-3-iodo-4-methoxypyridin-2-one Preparation Procedure

25                    A mixture of 2,4-dihydroxy-3-iodopyridine (1.0 eq),  $\text{Cs}_2\text{CO}_3$  (2.0 eq), MeI (10.0 eq) and anhydrous DMF was stirred at 40 °C for 72 h, and then the DMF and remaining MeI were evaporated. The residue was treated with aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , and the mixture was extracted five times with  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  extracts were treated with  $\text{MgSO}_4$ , filtered, and evaporated. The residue was recrystallized from hexanes/ $\text{CH}_2\text{Cl}_2$  to give 1-methyl-3-iodo-4-methoxypyridin-2-one.

30                    Method C

*N*-tert-Butoxycarbonyl-4-(1-methyl-4-methoxypyridin-2-one-3-yl)-L-phenylalanine Methyl Ester Preparation Procedure

The procedure of Morera and Ortar (*Syn. Lett.* 1997, (7), 1403-1405) was used to convert 1-methyl-3-iodo-4-methoxypyridin-2-one into *N*-tert-

5 butoxycarbonyl-4-(1-methyl-4-methoxypyridin-2-one-3-yl)-L-phenylalanine  
methyl ester.

#### Method D

##### BOC Removal Procedure

10 Anhydrous hydrochloride (HCl) gas was bubbled through a methanolic  
solution of the appropriate Boc-amino acid ester at 0°C for 15 minutes and  
the reaction mixture was stirred for three hours. The solution was  
concentrated to a syrup and dissolved in Et<sub>2</sub>O and reconcentrated. This  
15 procedure was repeated and the resulting solid was placed under high vacuum  
overnight.

#### Method E

##### Preparation of Dimethyl 2-Alkylmalonate

20 To a suspension of sodium hydride 60% dispersion in mineral oil (1.1  
eq) in anhydrous THF was added slowly with stirring dimethyl malonate (1.1  
eq), causing the evolution of gas. To the resulting solution was added a  
bromoalkane, iodoalkane, or trifluoromethanesulfonyloxyalkane (1.0 eq), and  
the mixture was heated to 50°C for 48 h, at which point TLC indicated  
consumption of the bromoalkane, iodoalkane, or  
25 trifluoromethanesulfonyloxyalkane. The mixture was diluted with diethyl  
ether and washed with 70% saturated sodium chloride. The organic extracts  
were treated with anhydrous magnesium sulfate, filtered, and evaporated to  
afford a dimethyl 2-alkylmalonate of sufficient purity for immediate  
conversion to a 5-alkyl-4,6-dihydroxypyrimidine.

#### Method F

##### Preparation of 5-Alkyl-4,6-dihydroxypyrimidine

30 To a diethyl 2-alkylmalonate or a dimethyl 2-alkylmalonate (1.0 eq) was  
added formamidine acetate (1.0 eq) and 25% sodium methoxide in methanol

(3.3 eq). The resulting slurry was stirred vigorously and heated to 60°C for 4 h, and then allowed to cool. The slurry was diluted with water, and acidified to pH = 2 by addition of HCl. The resulting precipitate was collected by filtration, washed with water, and dried under vacuum, to afford a 5-alkyl-4,6-dihydroxypyrimidine of sufficient purity for immediate conversion to a 5-alkyl-4,6-dichloropyrimidine.

#### Method G

##### Preparation of

##### 5-Alkyl-4,6-dichloropyrimidine or 5-Alkoxy-4-chloropyrimidine

To a 5-alkyl-4,6-dihydroxypyrimidine or a 5-alkoxy-4-hydroxypyrimidine (1.0 eq) were added phosphorus oxychloride (15.0 eq) and *N,N*-dimethylaniline (1.0 eq), and the mixture was heated to 100°C for 3 h, and then allowed to cool. The resulting solution was poured onto ice, and the mixture was extracted with dichloromethane. The organic extracts were treated with anhydrous magnesium sulfate, filtered, and evaporated to afford a 5-alkyl-4,6-dichloropyrimidine or a 5-alkoxy-4-chloropyrimidine of sufficient purity for immediate conversion to a 5-alkyl-4-*N*-alkylamino-6-chloropyrimidine or a 5-alkoxy-4-*N*-alkylaminopyrimidine.

#### Method H

##### Preparation of

##### 5-Alkyl-4-*N*-alkylamino-6-chloropyrimidine or

##### 5-Alkoxy-4-*N*-alkylaminopyrimidine

To a solution of a 5-alkyl-4,6-dichloropyrimidine or a 5-alkoxy-4-chloropyrimidine (1.0 eq) in ethanol were added an alkyl amine (1.2 eq, typically L-4-(*N,N*-dimethylcarbamoyloxy)-phenylalanine *tert*-butyl ester) and diisopropylethylamine (2.0 eq). The mixture was sealed in a pressure tube and heated to 120°C for 48 h, at which point TLC indicated consumption of the 5-alkyl-4,6-dichloropyrimidine or the 5-alkoxy-4-chloropyrimidine. The

5 mixture was evaporated, and the residue was partitioned between ethyl acetate and pH = 4.5 citrate buffer. The organic extracts were washed with saturated sodium chloride, treated with anhydrous magnesium sulfate, filtered, and evaporated. The residue was purified by chromatography on silica gel using ethyl acetate and hexanes to afford a pure 5-alkyl-4-*N*-alkylamino-6-chloropyrimidine or 5-alkoxy-4-*N*-alkylaminopyrimidine.

#### Method I

##### Preparation of 5-Alkyl-4-*N*-alkylaminopyrimidine (Procedure I)

15 A suspension of 5-alkyl-4-*N*-alkylamino-6-chloropyrimidine (1.0 eq), and an equal mass 10% palladium on carbon, and sodium bicarbonate (5.0 eq) in methanol was shaken under 55 psi hydrogen gas for 16 h, at which point TLC indicated consumption of the 5-alkyl-4-*N*-alkylamino-6-chloropyrimidine. The mixture was filtered through Celite and evaporated to give a residue, which was partitioned between ethyl acetate and 70% saturated sodium chloride. The organic extracts were treated with anhydrous magnesium sulfate, filtered, and evaporated. The residue was purified by chromatography on silica gel using ethyl acetate and hexanes to afford a pure 5-alkyl-4-*N*-alkylaminopyrimidine.

#### Method J

##### Preparation of 5-Alkyl-4-*N*-alkylaminopyrimidine (Procedure II)

25 A suspension of 5-alkyl-4-*N*-alkylamino-6-chloropyrimidine (1.0 eq), sodium acetate (10.0 eq), and zinc powder (20.0 eq) in a 9:1 mixture of acetic acid and water was stirred vigorously at 40°C for 72 h, at which point TLC indicated partial consumption of the 5-alkyl-4-*N*-alkylamino-6-chloropyrimidine. The supernatant solution was decanted from remaining zinc and evaporated. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate, and the organic extracts were treated with anhydrous magnesium sulfate, filtered, and evaporated. The residue was



5 purified by chromatography on silica gel using ethyl acetate and hexanes to afford a pure 5-alkyl-4-*N*-alkylaminopyrimidine.

#### Method K

##### Ester Hydrolysis Procedure II

10 To a chilled (0°C) THF/H<sub>2</sub>O solution (2:1, 5 - 10 mL) of the appropriate ester was added LiOH (1.1 equivalents). The temperature was maintained at 0°C and the reaction was complete in 1-3 hours. The reaction mixture was concentrated and the residue was taken up into H<sub>2</sub>O and the pH adjusted to 2-3 with aqueous HCl. The product was extracted with ethyl acetate and the combined organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to yield the desired acid.

#### Method L

##### Preparation of 5-Iodo-4(3H)-pyrimidinone

20 The procedure of Sakamoto *et. al.* (Chem. Pharm. Bull. **1986**, 34(7), 2719-2724) was used to convert 4(3H)-pyrimidinone into 5-iodo-4(3H)-pyrimidinone.

#### Example 1

##### **Synthesis of**

##### ***N*-(5-(2,2,2-trifluoroethyl)pyrimidin-4-yl)-L-4'-(1-methyl-4-methoxy-2-pyridon-3-yl)phenylalanine**

25 2,4-Dihydroxypyridine was converted via sequential application of methods A, B and C to give *N*-*tert*-butoxycarbonyl-4-(1-methyl-4-methoxypyridin-2-one-3-yl)-L-phenylalanine methyl ester. This compound was converted via method D to give 4-(1-methyl-4-methoxypyridin-2-one-3-yl)-L-phenylalanine methyl ester hydrochloride. 2,2,2-Trifluoroethyltriflate (prepared according to Gassman, et al. J. Org. Chem. 1984, 49(12), 2258-2273) was converted via sequential

30

5 application of methods E, F and G to give 4,6-dichloro-5-(2,2,2-trifluoroethyl)pyrimidine.

4-(1-Methyl-4-methoxypyridin-2-one-3-yl)-L-phenylalanine methyl ester hydrochloride and 4,6-dichloro-5-(2,2,2-trifluoroethyl)pyrimidine were coupled via method H, and the product transformed via sequential application of methods I and K to give the title compound.

Physical data were as follows:

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  = 8.4 (s), 8.06 (s), 7.66 (d), 7.25 – 7.18 (m), 6.45 (d), 5.12 – 5.08 (m), 3.94 – 3.9 (m), 3.77 (m), 3.49 (s), 3.35-3.17 (m).

$^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  = 173.7, 164.7, 163.2, 160.0, 155.8, 153.4, 138.7, 135.9, 131.9, 131.2, 130.3, 128.0, 113.7, 95.7, 55.2, 55.1, 36.5, 36.2, 31.1, 30.7.

### Biological Examples

#### Example A

#### *In vitro* Assay For Determining Binding of Candidate Compounds to VLA-4

An *in vitro* assay was used to assess binding of candidate compounds to  $\alpha_4\beta_1$  integrin. Compounds which bind in this assay can be used to assess VCAM-1 levels in biological samples by conventional assays (e.g., competitive assays). This assay is sensitive to  $\text{IC}_{50}$  values as low as about 1nM.

The activity of  $\alpha_4\beta_1$  integrin was measured by the interaction of soluble VCAM-1 with Jurkat cells (e.g., American Type Culture Collection Nos. TIB 152, TIB 153, and CRL 8163), a human T-cell line which expresses high levels of  $\alpha_4\beta_1$  integrin. VCAM-1 interacts with the cell surface in an  $\alpha_4\beta_1$  integrin-dependent fashion (Yednock, et al. J. Biol. Chem., 1995, 270:28740).

5           Recombinant soluble VCAM-1 was expressed as a chimeric fusion  
protein containing the seven extracellular domains of VCAM-1 on the N-  
terminus and the human IgG<sub>1</sub> heavy chain constant region on the C-terminus.  
The VCAM-1 fusion protein was made and purified by the manner described  
by Yednock, *supra*.

10           Jurkat cells were grown in RPMI 1640 supplemented with 10% fetal  
bovine serum, penicillin, streptomycin and glutamine as described by  
Yednock, *supra*.

15           Jurkat cells were incubated with 1.5 mM MnCl<sub>2</sub> and 5 µg/mL 15/7  
antibody for 30 minutes on ice. Mn<sup>+2</sup> activates the receptor to enhance ligand  
binding, and 15/7 is a monoclonal antibody that recognizes an  
activated/ligand occupied conformation of α<sub>4</sub>β<sub>1</sub> integrin and locks the  
molecule into this conformation thereby stabilizing the VCAM-1/α<sub>4</sub>β<sub>1</sub> integrin  
20           interaction. Yednock, et al., *supra*. Antibodies similar to the 15/7 antibody  
have been prepared by other investigators (Luque, et al, 1996, J. Biol. Chem.  
271:11067) and may be used in this assay.

25           Cells were then incubated for 30 minutes at room temperature with  
candidate compounds, in various concentrations ranging from 66 µM to 0.01  
µM using a standard 5-point serial dilution. 15 µL soluble recombinant  
VCAM-1 fusion protein was then added to Jurkat cells and incubated for 30  
minutes on ice. (Yednock et al., *supra*).

30           Cells were then washed two times and resuspended in PE-conjugated  
goat F(ab')<sub>2</sub> anti-mouse IgG Fc (Immunotech, Westbrook, ME) at 1:200 and  
incubated on ice, in the dark, for 30 minutes. Cells were washed twice and  
analyzed with a standard fluorescence activated cell sorter ("FACS") analysis  
as described in Yednock, et al., *supra*.

5           Compounds having an  $IC_{50}$  of less than about  $15\mu M$  possess binding  
affinity to  $\alpha_4\beta_1$ .

10           When tested in this assay, each of the compound prepared in the above  
examples has or is expected to have an  $IC_{50}$  of  $15\mu M$  or less (or is expected  
to be active *in vivo*).

#### Example B

##### ***In vitro* Saturation Assay For Determining Binding of Candidate Compounds to $\alpha_4\beta_1$**

15           The following describes an *in vitro* assay to determine the plasma levels  
needed for a compound to be active in the Experimental Autoimmune  
Encephalomyelitis ("EAE") model, described in the next example, or in other  
*in vivo* models.

20           Log-growth Jurkat cells are washed and resuspended in normal animal  
plasma containing  $20\mu g/ml$  of the 15/7 antibody (described in the above  
example).

25           The Jurkat cells are diluted two-fold into either normal plasma samples  
containing known candidate compound amounts in various concentrations  
ranging from  $66\mu M$  to  $0.01\mu M$ , using a standard 12 point serial dilution for  
a standard curve, or into plasma samples obtained from the peripheral blood  
of candidate compound-treated animals.

30           Cells are then incubated for 30 minutes at room temperature, washed  
twice with phosphate-buffered saline ("PBS") containing 2% fetal bovine  
serum and 1mM each of calcium chloride and magnesium chloride (assay  
medium) to remove unbound 15/7 antibody.

35

The cells are then exposed to phycoerythrin-conjugated goat F(ab')<sub>2</sub> anti-mouse IgG Fc (Immunotech, Westbrook, ME), which has been adsorbed for any non-specific cross-reactivity by co-incubation with 5% serum from the animal species being studied, at 1:200 and incubated in the dark at 4°C for 30 minutes.

Cells are washed twice with assay medium and resuspended in the same. They are then analyzed with a standard fluorescence activated cell sorter ("FACS") analysis as described in Yednock et al. J. Biol. Chem., 1995, 270:28740.

The data is then graphed as fluorescence versus dose, e.g., in a normal dose-response fashion. The dose levels that result in the upper plateau of the curve represent the levels needed to obtain efficacy in an *in vivo* model.

This assay may also be used to determine the plasma levels needed to saturate the binding sites of other integrins, such as the  $\alpha_9\beta_1$  integrin, which is the integrin most closely related  $\alpha_4\beta_1$  (Palmer et al, 1993, J. Cell Bio., 123:1289). Such binding is predictive of *in vivo* utility for inflammatory conditions mediated by  $\alpha_9\beta_1$  integrin, including by way of example, airway hyper-responsiveness and occlusion that occurs with chronic asthma, smooth muscle cell proliferation in atherosclerosis, vascular occlusion following angioplasty, fibrosis and glomerular scarring as a result of renal disease, aortic stenosis, hypertrophy of synovial membranes in rheumatoid arthritis, and inflammation and scarring that occur with the progression of ulcerative colitis and Crohn's disease.

Accordingly, the above-described assay may be performed with a human colon carcinoma cell line, SW 480 (ATTC #CCL228) transfected with cDNA encoding  $\alpha_9$  integrin (Yokosaki et al., 1994, J. Biol. Chem., 269:26691), in

5 place of the Jurkat cells, to measure the binding of the  $\alpha_9\beta_1$  integrin. As a control, SW 480 cells which express other  $\alpha$  and  $\beta_1$  subunits may be used.

10 Accordingly, another aspect of this invention is directed to a method for treating a disease in a mammalian patient, which disease is mediated by  $\alpha_9\beta_1$ , and which method comprises administering to said patient a therapeutically effective amount of a compound of this invention. Such compounds are preferably administered in a pharmaceutical composition described herein above. Effective daily dosing will depend upon the age, weight, condition of the patient which factors can be readily ascertained by the attending clinician. However, in a preferred embodiment, the compounds are administered from about 20 to 500  $\mu\text{g/kg}$  per day.

#### Example C

##### ***In vivo* Evaluation**

20 The standard multiple sclerosis model, Experimental Autoimmune (or Allergic) Encephalomyelitis ("EAE"), was used to determine the effect of candidate compounds to reduce motor impairment in rats or guinea pigs. Reduction in motor impairment is based on blocking adhesion between leukocytes and the endothelium and correlates with anti-inflammatory activity in the candidate compound. This model has been previously described by Keszthelyi et al., Neurology, 1996, 47:1053-1059, and measures the delay of onset of disease.

30 Brains and spinal cords of adult Hartley guinea pigs were homogenized in an equal volume of phosphate-buffered saline. An equal volume of Freund's complete adjuvant (100 mg *mycobacterium tuberculosis* plus 10 ml Freund's incomplete adjuvant) was added to the homogenate. The mixture was emulsified by circulating it repeatedly through a 20 ml syringe with a peristaltic pump for about 20 minutes.

35

5

Female Lewis rats (2-3 months old, 170-220 g) or Hartley guinea pigs (20 day old, 180-200 g) were anesthetized with isoflurane and three injections of the emulsion, 0.1 ml each, were made in each flank. Motor impairment onset is seen in approximately 9 days.

10

Candidate compound treatment began on Day 8, just before onset of symptoms. Compounds were administered subcutaneously ("SC"), orally ("PO") or intraperitoneally ("IP"). Doses were given in a range of 10mg/kg to 200 mg/kg, bid, for five days, with typical dosing of 10 to 100 mg/kg SC, 10 to 50 mg/kg PO, and 10 to 100 mg/kg IP.

15

Antibody GG5/3 against  $\alpha_4\beta_1$  integrin (Keszthelyi et al., Neurology, 1996, 47:1053-1059), which delays the onset of symptoms, was used as a positive control and was injected subcutaneously at 3 mg/kg on Day 8 and 11.

20

Body weight and motor impairment were measured daily. Motor impairment was rated with the following clinical score:

25

0	no change
1	tail weakness or paralysis
2	hindlimb weakness
3	hindlimb paralysis
4	moribund or dead

30

A candidate compound was considered active if it delayed the onset of symptoms, e.g., produced clinical scores no greater than 2 or slowed body weight loss as compared to the control.

35

Example D

**Asthma Model**

Inflammatory conditions mediated by  $\alpha_4\beta_1$  integrin include, for example, airway hyper-responsiveness and occlusion that occurs with chronic asthma. The following describes an asthma model which can be used to study the *in vivo* effects of the compounds of this invention for use in treating asthma.

Following the procedures described by Abraham et al, J. Clin. Invest, 93:776-787 (1994) and Abraham et al, Am J. Respir Crit Care Med, 156:696-703 (1997), both of which are incorporated by reference in their entirety. Compounds of this invention are formulated into an aerosol and administered to sheep which are hypersensitive to *Ascaris suum* antigen. Compounds which decrease the early antigen-induced bronchial response and/or block the late-phase airway response, e.g., have a protective effect against antigen-induced late responses and airway hyper-responsiveness ("AHR"), are considered to be active in this model.

Allergic sheep which are shown to develop both early and late bronchial responses to inhaled *Ascaris suum* antigen are used to study the airway effects of the candidate compounds. Following topical anesthesia of the nasal passages with 2% lidocaine, a balloon catheter is advanced through one nostril into the lower esophagus. The animals are then intubated with a cuffed endotracheal tube through the other nostril with a flexible fiberoptic bronchoscope as a guide.

Pleural pressure is estimated according to Abraham (1994). Aerosols (see formulation below) are generated using a disposable medical nebulizer that provides an aerosol with a mass median aerodynamic diameter of  $3.2\ \mu\text{m}$  as determined with an Andersen cascade impactor. The nebulizer is connected to a dosimeter system consisting of a solenoid valve and a source



5 of compressed air (20 psi). The output of the nebulizer is directed into a  
plastic T-piece, one end of which is connected to the inspiratory port of a  
piston respirator. The solenoid valve is activated for 1 second at the  
beginning of the inspiratory cycle of the respirator. Aerosols are delivered at  
V<sub>T</sub> of 500 ml and a rate of 20 breaths/minute. A 0.5% sodium bicarbonate  
10 solution only is used as a control.

To assess bronchial responsiveness, cumulative concentration-response  
curves to carbachol can be generated according to Abraham (1994).  
Bronchial biopsies can be taken prior to and following the initiation of  
15 treatment and 24 hours after antigen challenge. Bronchial biopsies can be  
performed according to Abraham (1994).

An *in vitro* adhesion study of alveolar macrophages can also be  
performed according to Abraham (1994), and a percentage of adherent cells is  
20 calculated.

#### Aerosol Formulation

A solution of the candidate compound in 0.5% sodium bicarbonate/saline  
(w/v) at a concentration of 30.0 mg/mL is prepared using the following  
25 procedure:

#### A. Preparation of 0.5% Sodium Bicarbonate / Saline Stock Solution: 100.0 mL

Ingredient	Gram / 100.0 mL	Final Concentration
Sodium Bicarbonate	0.5 g	0.5%
Saline	q.s. ad 100.0 mL	q.s. ad 100%

Procedure:

1. Add 0.5g sodium bicarbonate into a 100 mL volumetric flask.
2. Add approximately 90.0 mL saline and sonicate until dissolved.
3. Q.S. to 100.0 mL with saline and mix thoroughly.

B. Preparation of 30.0 mg/mL Candidate Compound: 10.0 mL

Ingredient	Gram / 10.0 mL	Final Concentration
Candidate Compound	0.300 g	30.0 mg/mL
0.5 % Sodium Bicarbonate / Saline Stock Solution	q.s. ad 10.0 mL	q.s ad 100%

Procedure:

1. Add 0.300 g of the candidate compound into a 10.0 mL volumetric flask.
2. Add approximately 9.7 mL of 0.5 % sodium bicarbonate / saline stock solution.
3. Sonicate until the candidate compound is completely dissolved.
4. Q.S. to 10.0 mL with 0.5 % sodium bicarbonate / saline stock solution and mix thoroughly.

Using a conventional oral formulation, compounds of this invention would be active in this model.

Example E  
**Allograft Model**

Allograft rejection, associated with infiltration of inflammatory cells, is the leading obstacle to long-term allograft survival. Cell surface adhesion molecules facilitate alloantigen recognition *in vitro* and may be critical for

5 lymphocyte traffic *in vivo*. The following describes a model which can be used to study the *in vivo* effects of the compounds of this invention in the control of allograft rejection.

10 The following procedures are described in Coito et al., *Transplantation* (1998) **65(6)**:699-706 and in Korom et al., *Transplantation* (1998) **65(6)**:854-859, both of which are incorporated by reference in their entirety.

15 Following the procedures described in Coito and Korom, male adult rats weighing approximately 200 - 250 g are used in this model. Lewis rats are used as the recipients of cardiac allografts from Lewis X Brown Norway rats. Hearts are transplanted into the abdominal great vessels using standard microvascular techniques.

20 A candidate compound is administered to the transplant recipient in a suitable pharmaceutical carrier for a 7-day course of treatment starting the day of the engraftment. Doses range from 0.3 to 30 mg/kg/day. Control recipients receive the pharmaceutical carrier only. The rats are euthanized and their cardiac allografts are analyzed as described in Coito and Korom.

25 Using conventional formulations, compounds of this invention would be active in this model.